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Schwartz's **PRINCIPLES OF SURGERY**

TENTH EDITION

F. Charles Brunickardi

Dana K. Andersen • Timothy R. Billiar

David L. Dunn • John G. Hunter

Jeffrey B. Matthews • Raphael E. Pollock

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Schwartz's Principles of Surgery

Tenth Edition

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Schwartz's Principles of Surgery

Tenth Edition

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Stephen Lowry, MD, MBA (1947-2011)

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The tenth edition of *Schwartz's Principles of Surgery* is dedicated to the late Dr. Stephen Lowry, consummate surgeon-scientist, educator, colleague, mentor, and long-time contributor to *Schwartz's Principles of Surgery*. At the time of his death, Dr. Lowry served as Richard Harvey Professor and Chair of the Department of Surgery and Senior Associate Dean for Education at the Rutgers-Robert Wood Johnson Medical School (RWJMS) in New Brunswick, New Jersey. He was the inaugural holder of the Richard Harvey Professorship at RWJMS, which honors excellence in innovative teaching and exemplified his absolute dedication to medical education. Dr. Lowry's dedicated and distinguished surgical career produced valuable contributions to both scientific knowledge and patient care, including his seminal investigations utilizing the human endotoxemia model that defined important aspects of the host inflammatory response following injury. His investigations had been supported by continuous National Institute of Health (NIH) funding for more than 25 years and were recognized by the coveted Method to

Extend Research in Time (MERIT) award from the NIH. He authored more than 400 scientific publications and was the recipient of numerous honors that recognized his academic achievements. Although Dr. Lowry received many accolades and awards throughout his career, he was first and foremost an enthusiastic teacher and sincere supporter of people, their goals, and their lives. Dr. Lowry genuinely enjoyed listening, learning, and sharing his knowledge and did so with a depth of feeling that inspired and encouraged those around him. As his wife Susette wrote, "Steve knew he would be remembered for his professional accomplishments, but never imagined he would be honored and missed for his personality and style that set him apart from the rest. The world really was a better place with Steve in it!" The loss of his warmth, professionalism, intellect, and enthusiasm for medical education will be greatly missed.

**Siobhan Corbett, MD, and the editors of
Schwartz's Principles of Surgery, Tenth edition**



Robert S. Dorian, MD, MBA (1954-2014)

Photo provided by Saint Barnabas Medical Center. Used with permission.

The Editors of *Schwartz's Principles of Surgery* wish to dedicate this tenth edition to the memory of Dr. Robert S. Dorian, the sole author of the "Anesthesia" chapter in the last three editions. Dr. Dorian was born in Philadelphia and grew up in Livingston, New Jersey where his father was a prominent gynecologist. He received his undergraduate degree in Physics and Music from Tufts University in Boston while at the same time studying piano at the New England Conservatory of Music. Bob received his medical education at Rutgers Medical School in Piscataway, New Jersey. After completing an internship in surgery at Downstate Medical Center in Brooklyn, he trained in anesthesiology at Weill Cornell Medical College and New York Hospital in New York City. He completed a fellowship in pediatric anesthesiology at Boston Children's Hospital and Harvard Medical School. After his training, Bob established practice at the St. Barnabas Medical Center and rose to become the Chairman of the Department of Anesthesiology, a position he held for 14 years until his death. He was highly respected on both a national and international basis as an outstanding chairman.

Bob was a consummate anesthesiologist, educator, mentor, and wonderful friend. He was the greatest of clinical anesthesiologists and was dedicated to providing the highest level of care to his patients. He was an extraordinary teacher and as the Program Director of the St. Barnabas anesthesia residency program for ten years, he trained

scores of residents. His residents adored him because of the tremendous amount of attention he gave to each resident to assure they were highly trained in their craft and that they were placed in the top fellowships around the nation. Bob was also an incredibly gifted musician, scholar, and thinker. His intellect, humanity, and humor were inspiring to everyone who knew him. Bob was respected on an international basis for his humanitarian work with frequent medical missions to underserved populations around the world. In this endeavor, he was often accompanied by his wife, Linda, and their daughters, Rose and Zoe.

Dr. Dorian had a most special gift and that was to bring out the best in every person that he met and make them feel very special. He lit up every room and made each encounter an occasion to remember. Having a conversation with Bob was one of life's great pleasures. Colleagues, nurses, and patients would look forward to his arrival because he would make them laugh and brighten their day. He was loved by all and will be sorely missed. Bob's memory and legacy will live on in the thousands of patients that he cared for, in the academic programs that he fostered, in the generations of anesthesiologists that he trained, and in his remarkable family. His words and intellect will be preserved in this textbook of surgery.

**James R. Macho, MD, FACS, and the editors of
Schwartz's Principles of Surgery, Tenth edition**

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Foreword

The adjective “tenth” connotes a milestone, and, in the case of a “tenth edition” of a textbook, it is evidence of readership acceptability. This continued reader response would evoke parental pride from those who generated the original publication more than 45 years ago. I can still vividly recall the meeting in New York City at which John DeCarville, an editor at McGraw-Hill, brought together David M. Hume, Richard C. Lillehei, G. Thomas Shires, Edward H. Storer, Frank C. Spencer, and me to create a new surgical textbook. The new surgical publication was to serve as a companion to Harrison’s recently introduced medical textbook. The favorable reception of the first edition was most encouraging. The consistency of style and the deliberate inclusion of 52 chapters to allow for review of one chapter a week throughout the year were particularly appealing. Subsequent to the initial publication and following the tragic and premature deaths of Dr. Lillehei, Dr. Hume, and Dr. Storer, Dr. Shires, Dr. Spencer, and I were privileged to shepherd six additional editions over the ensuing 35 years. Under the direction of Dr. F. Charles Brunicaudi and his associate editors, a new vitality was infused over the three most recent editions.

The ten editions, as they are considered in sequence, serve as a chronicle of the dramatic evolution that has occurred in surgery over the past half century. Those, who have been charged with providing current information to the readership, have had to filter and incorporate extraordinary and unanticipated scientific breakthroughs and technical innovations. At the time of the genesis of the first edition, success had not been achieved in cardiac, hepatic, or intestinal transplantation. Adjuvant therapy for a broad variety of malignancies was in its infancy. Minimally invasive surgery would not become a reality for two decades. On the other side of the spectrum, operative procedures that occupied the focus of symposia have slipped into obscurity. Vagotomy for peptic ulcer has become a rarity, as a consequence of an appreciation of

the role of *Helicobacter pylori* and the efficacy of proton pump inhibitors. Surgical procedures to decompress portal hypertension in the treatment of bleeding esophagogastric varices have essentially disappeared from the operating room schedule. They have been replaced by transjugular intrahepatic portosystemic shunt (TIPS) and the liberal application of hepatic transplantation.

As Bob Dylan pointed out, “The Times They Are A-changin.” And they most assuredly will continue to change, and at an unanticipated rate. The scientific basis for the practice of surgery is increasing at an ever accelerating pace, and the technologic improvements and breakthroughs are equally extraordinary. The dissemination of the expansion of knowledge has resulted in a shrinking of the globe, necessitating an extension or adaptation of the more modern approaches to underdeveloped nations and underprivileged populations. Global medicine has become a modern concern. The importance of internationalism is manifest in the clinical trials and data acquisition provided by our surgical colleagues on the other sides of the oceans that surround us. It is therefore appropriate that a more international flavor has been developed for *Principles of Surgery* related both to citations and contributors. A distinct consideration of global medicine and, also, the qualities of leadership in surgery that must be nurtured are evidence of the editorial credo of “maintaining modernization” and “anticipating the future.”

As the editors and contributors continue to provide the most up-to-date information with a clarity that facilitates learning, it is the hope that the seed, which was planted almost a half century ago, will continue to flourish and maintain the approval of its audience.

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Preface

Each new edition of this book is approached by the editorial team with a dual vision keeping a dedicated eye affixed to the foundations of surgery while bringing into sharper focus on new and emerging elements. We are entering into a spectacular era of surgery in which the highest quality of care is merging with minimally invasive surgery, robotic surgery, the use of supercomputers, and personalized genomic surgery, all designed to improve the outcomes and quality of life for our patients. With these advances in mind, several new chapters have been added and all previous chapters have been updated with an emphasis on evidence-based, state-of-the-art surgical care. While this tried-and-true method remains the basis for upholding and maintaining the superb efforts and achievements of Dr. Seymour Schwartz and previous co-editors and contributors, this edition expands its vision to see beyond the operating theater and takes a look at the making of a surgeon as a whole, with the addition of the chapter, Fundamental Principles of Leadership Training in Surgery. Surely excellence in craft must be mastered and equal importance must also be given to the nontechnical training of what it means to be a leader of a surgical team.

To this effort, the editors were keen to include as the first chapter in this edition a comprehensive review of leadership methods and ideologies as well as underscoring the importance of instituting a formal leadership-training program for residents that emphasizes mentoring. Our own paths as surgeons have been defined by the mentoring

relationship and we have undoubtedly benefitted greatly from the efforts of our mentors; we sincerely hope that those with whom we have entered into this time-honored tradition have reaped the benefit as well. Simply stated, leadership skills can and should be taught to surgical trainees and in doing so this will help them improve quality of care.

The editors are thankful that this text is a relied-on source for training and crafting surgeons on a global basis. This is due in large part to the extraordinary efforts of our contributors, the leaders in their fields, who not only do so to train up-and-coming surgeons, but to impart their knowledge and expertise to the benefit of patients worldwide. The recent inclusion of many international authors to the chapters within is ultimately a testament to mentorship, albeit on a broader scale, and we thank them all, both near and far.

To our fellow editorial board members who have tirelessly devoted their time and knowledge to the integrity and excellence of their craft and this textbook, we extend our gratitude and thanks. We are so thankful to Brian Belval, Christie Naglieri, and all at McGraw-Hill for the continued belief in and support of this textbook. We wish to thank Katie Elsbury for her dedication to the organization and editing of this textbook. Last, we would like to thank our families who are the most important contributors of all.

F. Charles Brunicardi, MD, FACS

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Preface to the First Edition

The *raison d'être* for a new textbook in a discipline which has been served by standard works for many years was the Editorial Board's initial conviction that a distinct need for a modern approach in the dissemination of surgical knowledge existed. As incoming chapters were reviewed, both the need and satisfaction became increasingly apparent and, at the completion, we felt a sense of excitement at having the opportunity to contribute to the education of modern and future students concerned with the care of surgical patients.

The recent explosion of factual knowledge has emphasized the need for a presentation which would provide the student an opportunity to assimilate pertinent facts in a logical fashion. This would then permit correlation, synthesis of concepts, and eventual extrapolation to specific situations. The physiologic bases for diseases are therefore emphasized and the manifestations and diagnostic studies are considered as a reflection of pathophysiology. Therapy then becomes logical in this schema and the necessity to regurgitate facts is minimized. In appreciation of the impact which *Harrison's Principles of Internal Medicine* has had, the clinical manifestations of the disease processes are considered in detail for each area. Since the operative procedure represents the one element in the therapeutic armamentarium unique to the surgeon, the indications, important technical considerations, and complications receive appropriate emphasis. While we appreciate that a textbook cannot hope to incorporate an atlas of surgical

procedures, we have provided the student a single book which will satisfy the sequential demands in the care and considerations of surgical patients.

The ultimate goal of the Editorial Board has been to collate a book which is deserving of the adjective "modern." We have therefore selected as authors dynamic and active contributors to their particular fields. The *au courant* concept is hopefully apparent throughout the entire work and is exemplified by appropriate emphasis on diseases of modern surgical interest, such as trauma, transplantation, and the recently appreciated importance of rehabilitation. Cardiovascular surgery is presented in keeping with the exponential strides recently achieved.

There are two major subdivisions to the text. In the first twelve chapters, subjects that transcend several organ systems are presented. The second portion of the book represents a consideration of specific organ systems and surgical specialties.

Throughout the text, the authors have addressed themselves to a sophisticated audience, regarding the medical student as a graduate student, incorporating material generally sought after by the surgeon in training and presenting information appropriate for the continuing education of the practicing surgeon. The need for a text such as we have envisioned is great and the goal admittedly high. It is our hope that this effort fulfills the expressed demands.

Seymour I. Schwartz, MD, FACS

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Part

Basic Considerations

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1 chapter

Fundamental Principles of Leadership Training in Surgery

Amy L. Hill, James Wu, Mark D. Girgis, Danielle Hsu, Areti Tillou, James Macho, Vishad Nabili, and F. Charles Brunicardi

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		Leadership Styles		

INTRODUCTION

The field of surgery has evolved greatly from its roots, and surgical practice now requires the mastery of modern leadership principles and skills as much as the acquisition of medical knowledge and surgical technique. Historically, surgeons took sole responsibility for their patients and directed proceedings in the operating room with absolute authority, using a command-and-control style of leadership. Modern surgical practice has now evolved from single provider-based care toward a team-based approach, which requires collaborative leadership skills. Surgical care benefits from the collaboration of surgeons, anesthesiologists, internists, radiologists, pathologists, radiation oncologists, nurses, pharmacists, social workers, therapists, hospital staff, and administrators. Occupying a central role on the healthcare team, surgeons¹ have the potential to improve patient outcomes, reduce medical errors, and improve patient satisfaction through their leadership of the multidisciplinary team.

1► Thus, in the landscape of modern healthcare systems, it is imperative that surgical training programs include formal instruction on leadership principles and skills to cultivate their trainees' leadership capabilities.

Many medical and surgical communities, including residency training programs, acknowledge the need for improved physician leadership.² Surgical trainees identify leadership skills as important, but report themselves as "not competent" or "minimally competent" in this regard.^{2,3} While a small number of surgical training programs have implemented formal curriculum focused on teaching leadership principles, it is now imperative that all surgical training programs teach these important skills to their trainees.^{4,5} Interviews of academic chairpersons identified several critical leadership success factors,⁶ including mastery of visioning, communication, change management, emotional intelligence, team building, business skills, personnel management, and systems thinking. These chairpersons stated that the ability of emotional intelligence was "fundamental to their success and its absence the cause of their failures," regardless of medical knowledge.⁶ Thus, training programs need to include leadership training to prepare trainees for success in modern healthcare delivery.

In the United States, the Accreditation Council for Graduate Medical Education (ACGME) has established six

core competencies—patient care, medical knowledge, practice-based learning and improvement, interpersonal and communication skills, professionalism, and systems-based practice (Table 1-1)⁴—that each contain principles of leadership. The ACGME has mandated the teaching of these core competencies but has not established a formal guide on how to teach the leadership skills described within the core competencies. Therefore, this chapter offers a review of fundamental principles of leadership and an introduction of the concept of a leadership training program for surgical trainees.

DEFINITIONS OF LEADERSHIP

Many different definitions of leadership have been described. Former First Lady Rosalynn Carter once observed that, "A leader takes people where they want to go. A *great* leader takes people where they don't necessarily want to go, but where they ought to be." Leadership does not always have to come from a position of authority. Former American president John Quincy Adams stated, "If your actions inspire others to dream more, learn more, do more, and become more, you are a leader." Another definition is that leadership is the process of using social influence to enlist the aid and support of others in a common task.⁷

FUNDAMENTAL PRINCIPLES OF LEADERSHIP

Clearly, leadership is a complex concept. Surgeons should strive to adopt leadership qualities that provide the best outcomes for their patients, based on the following fundamental principles.

Vision

The first and most fundamental principle of leadership is to establish a vision that people can live up to, thus providing direction and purpose to the constituency. Creating a vision is a declaration of the near future that inspires and conjures motivation.⁸ A classic example of a powerful vision that held effective impact is President Kennedy's declaration in 1961 that "... this nation should commit itself to achieving the goal, before this decade is out, of landing a man on the moon and returning him safely to the earth." Following his declaration of this vision with a timeline to achieve it, the United States mounted a remarkable unified effort, and by the end of the decade, Neil Armstrong

Key Points

- 1▶ Effective surgical leadership improves patient care.
- 2▶ A fundamental principle of leadership is to provide a vision that people can live up to, thereby providing direction and purpose to the constituency.
- 3▶ Surgical leaders have the willingness to lead through an active and passionate commitment to the vision.
- 4▶ Surgical leaders have the willingness to commit to lifelong learning.
- 5▶ Surgical leaders have the willingness to communicate effectively and resolve conflict.
- 6▶ Surgical leaders must practice effective time management.
- 7▶ Different leadership styles are tools to use based on the team dynamic.
- 8▶ Surgical trainees can be taught leadership principles in formal leadership training programs to enhance their ability to lead.
- 9▶ Mentorship provides wisdom, guidance, and insight essential for the successful development of a surgical leader.

took his famous walk and the vision had been accomplished (Fig. 1-1).

On a daily basis, surgeons are driven by a powerful vision: the vision that our surgical care will improve patients' lives. The great surgical pioneers, such as Hunter, Lister (Fig. 1-2), Halsted, von Langenbeck, Billroth, Kocher (Fig. 1-3), Carrel, Gibbon, Blalock, Wangenstein, Moore, Rhoads, Huggins, Murray, Kountz, Longmire, Starzl, and DeBakey (Fig. 1-4), each possessed visions that revolutionized the field of surgery. In the nineteenth century, Joseph Lister changed the practice of surgery with his application of Pasteur's germ theory. He set a young boy's open compound leg fracture, a condition with a 90% mortality rate at that time, using carbolic acid dressings and aseptic surgical technique. The boy recovered, and Lister gathered nine more patients. His famous publication on the use of aseptic technique introduced the modern era of sterile technique. Emil Theodor Kocher was the first to master the thyroidectomy, thought to be an impossible operation at the time, and went on to perform thousands of thyroidectomies with a mortality of less than 1%. He was awarded the Nobel Prize in Physiology or Medicine in 1909 for describing the thyroid's physiologic role in metabolism. Michael E. DeBakey's powerful vision led to the development of numerous groundbreaking procedures that helped pioneer the field of cardiovascular surgery. For example, envisioning an artificial

artery for arterial bypass operations, Dr. DeBakey invented the Dacron graft, which has helped millions of patients suffering from vascular disease and enabled the development of endovascular surgery. Dr. Frederick Banting, the youngest recipient of the Nobel Prize in Physiology or Medicine, had a vision to discover the biochemical link between diabetes and glucose homeostasis. His vision and perseverance led to the discovery of insulin.⁹ In retrospect, the power and clarity of their visions were remarkable, and their willingness and dedication were inspiring. By studying their careers and accomplishments, surgical trainees can appreciate the potential impact of a well-developed vision.

Leaders must learn to develop visions to provide direction for their team. The vision can be as straightforward as providing quality of care or as lofty as defining a new field of surgery. One can start developing their vision by brainstorming the answers to two simple questions: "Which disease needs to be cured?" and "How can it be cured?"¹⁰ The answers represent a vision and should be recorded succinctly in a laboratory notebook or journal. Committing pen to paper enables the surgical trainee to define their vision in a manner that can be shared with others.

Willingness

The Willingness Principle represents the active commitment of the leader toward their vision. A surgical leader must be willing

Table 1-1

Accreditation Council for Graduate Medical Education core competencies

CORE COMPETENCY	DESCRIPTION
Patient care	To be able to provide compassionate and effective healthcare in the modern-day healthcare environment
Medical knowledge	To effectively apply current medical knowledge in patient care and to be able to use medical tools (i.e., PubMed) to stay current in medical education
Practice-based learning and improvement	To critically assimilate and evaluate information in a systematic manner to improve patient care practices
Interpersonal and communication skills	To demonstrate sufficient communication skills that allow for efficient information exchange in physician-patient interactions and as a member of a healthcare team
Professionalism	To demonstrate the principles of ethical behavior (i.e., informed consent, patient confidentiality) and integrity that promote the highest level of medical care
Systems-based practice	To acknowledge and understand that each individual practice is part of a larger healthcare delivery system and to be able to use the system to support patient care

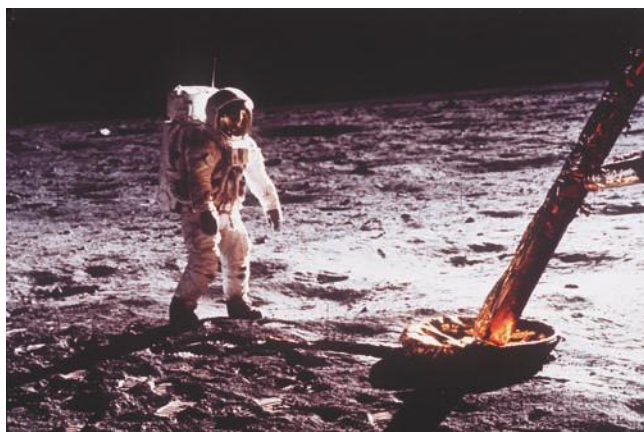


Figure 1-1. Apollo 11 Lunar Module moon walk. Astronaut Edwin “Buzz” Aldrin walks by the footpad of the Apollo 11 Lunar Module, July 1969. (Reproduced with permission from AP Photo/NASA. © 2014 The Associated Press.)

to lead, commit to lifelong learning, communicate effectively, and resolve conflict.

To Lead. A key characteristic of all great leaders is the willingness to serve as the leader. Dr. Martin Luther King, Jr., who championed the civil rights movement with a powerful vision of equality for all based on a commitment to non-violent methods,¹¹ did so at a time when his vocalization of this vision ensured harassment, imprisonment, and threats of violence against himself, his colleagues, and his family and friends (Fig. 1-5). King, a young, highly educated pastor, had the security of employment and family, yet was willing to accept enormous responsibility and personal risk and did so in order to lead a nation toward his vision of civil rights, for which he was awarded the Nobel Peace Prize in 1964. Steve Jobs, co-founder of Apple Inc., chose to remain in his position as chief executive officer (CEO) to pursue his vision of perfecting the personal computer at great personal expense. He described this experience as “. . . rough, really rough, the worst time in my life . . . I would go to work at 7 a.m. and I’d get back at 9 at night, and the kids would be in bed. And I couldn’t speak, I literally couldn’t, I was so exhausted . . . It got close

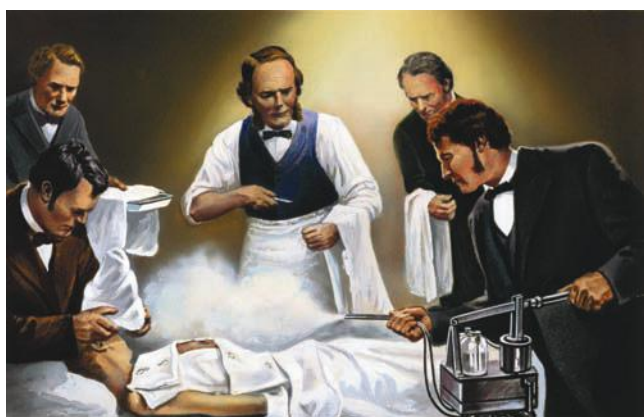
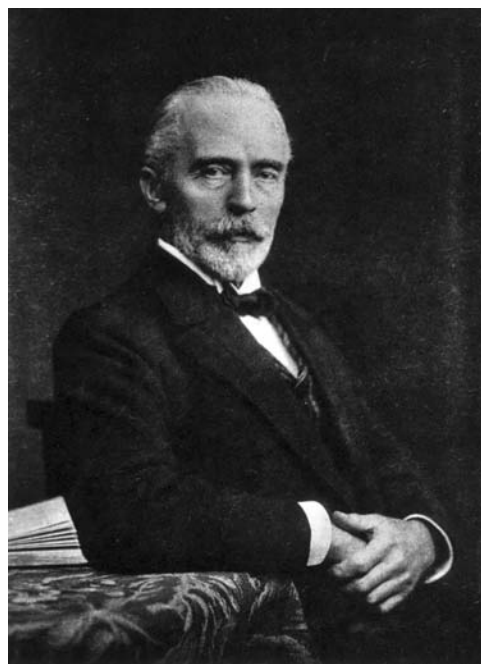


Figure 1-2. Joseph Lister directing use of carbolic acid spray in one of his earliest antiseptic surgical operations, circa 1865. (Copyright Bettmann/Corbis/AP Images.)



Emil Theodor Kocher

Figure 1-3. Emil Theodor Kocher. (Courtesy of the National Library of Medicine.)

to killing me.”¹² Both individuals demonstrated a remarkable tenacity and devotion to their vision.

Willingness to lead is a necessity in any individual who desires to become a surgeon. By entering into the surgical theater, a surgeon accepts the responsibility to care for and operate on patients despite the risks and burdens involved. They do so, believing fully in the improved quality of life that can be achieved. Surgeons must embrace the responsibility of leading surgical teams that care for their patients, as well as leading surgical trainees to become future surgeons. A tremendous sacrifice is required for the opportunity to learn patient care. Surgical trainees accept the hardships of residency with its

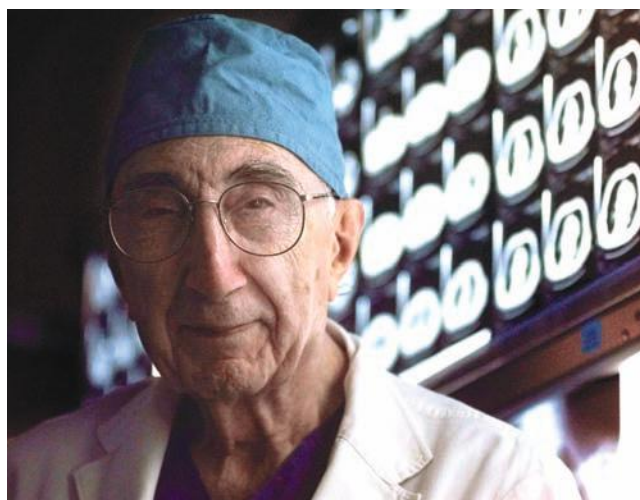


Figure 1-4. Michael E. DeBakey. (Reproduced with permission from AP Photo/David J. Phillip. © 2014 The Associated Press.)

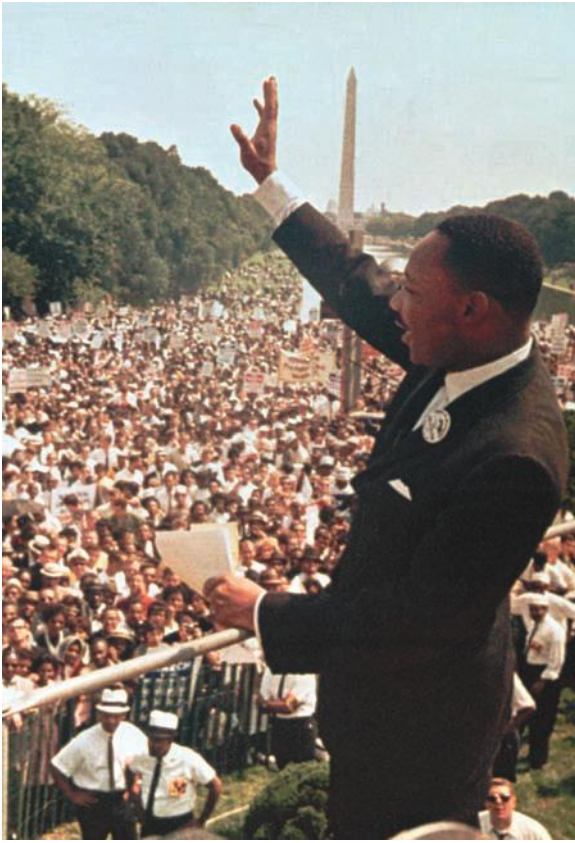


Figure 1-5. Dr. Martin Luther King, Jr. acknowledges the crowd at the Lincoln Memorial for his “I Have a Dream” speech during the March on Washington, D.C., August 28, 1963. (Reproduced with permission from AP Photo. © 2014 The Associated Press.)

accompanying steep learning curve, anxiety, long work hours, and time spent away from family and friends. The active, passionate commitment to excellent patient care reflects a natural willingness to lead based on altruism and a sense of duty toward those receiving care. Thus, to ensure delivery of the utmost level of care, surgical trainees should commit to developing and refining leadership skills. These skills include a commitment to lifelong learning, effective communication, and conflict resolution.

To Learn. Surgeons and surgical trainees, as leaders, must possess willingness to commit to continuous learning. Modern surgery is an ever-changing field with dynamic and evolving healthcare systems and constant scientific discovery and innovation. Basic and translational science relating to surgical care is growing at an exponential rate. The sequencing of the human genome and the enormous advances in molecular biology and signaling pathways are leading to the transformation of personalized medicine and surgery in the twenty-first century (see Chap. 15).¹³ Performing prophylactic mastectomies with immediate reconstruction for *BRCA1* mutations and thyroidectomies with thyroid hormone replacement for *RET* proto-oncogene mutations are two of many examples of genomic information guiding surgical care. Technologic advances in minimally invasive surgery and robotic surgery as well as electronic records and other information technologies are revolutionizing the craft of surgery. The expansion of minimally invasive and endovascular surgery over the past three decades required surgeons to retrain

in new techniques using new skills and equipment. In this short time span, laparoscopy and endovascular operations are now recognized as the standard of care for many surgical diseases, resulting in shorter hospital stay, quicker recovery, and a kinder and gentler manner of practicing surgery. Remarkably, during the last century, the field of surgery has progressed at an exponential pace and will continue to do so with the advent of using genomic analyses to guide personalized surgery, which will transform the field of surgery this century. Therefore, surgical leadership training should emphasize and facilitate the continual pursuit of knowledge.

Fortunately, surgical organizations and societies provide surgeons and surgical trainees a means to acquire new knowledge on a continuous basis. There are numerous local, regional, national, and international meetings of surgical organizations that provide ongoing continuing medical education credits, also required for the renewal of most medical licenses. The American Board of Surgery requires all surgeons to complete meaningful continuing medical education to maintain certification.¹⁴ These societies and regulatory bodies enable surgeons and surgical trainees to commit to continual learning, and ensure their competence in a dynamic and rapidly growing field.

Surgeons and trainees now benefit from the rapid expansion of web-based education as well as mobile handheld technology. These are powerful tools to minimize nonproductive time in the hospital and make learning and reinforcement of medical knowledge accessible. Currently web-based resources provide quick access to a vast collection of surgical texts, literature, and surgical videos. Surgeons and trainees dedicated to continual learning should be well versed in the utilization of these information technologies to maximize their education. The next evolution of electronic surgical educational materials will likely include simulation training similar to laparoscopic and Da Vinci device training modules. The ACGME, acknowledging the importance of lifelong learning skills and modernization of information delivery and access methods, has included them as program requirements for residency accreditation.

To Communicate Effectively. The complexity of modern healthcare delivery systems requires a higher level and collaborative style of communication. Effective communication directly impacts patient care. In 2000, the U.S. Institute of Medicine published a work titled, *To Err Is Human: Building a Safer Health System*, which raised awareness concerning the magnitude of medical errors. This work showcased medical errors as the eighth leading cause of death in the United States with an estimated 100,000 deaths annually.¹⁵ Subsequent studies examining medical errors have identified communication errors as one of the most common causes of medical error.^{16,17} In fact, the Joint Commission identifies miscommunication as the leading cause of sentinel events. Information transfer and communication errors cause delays in patient care, waste surgeon and staff time, and cause serious adverse patient events.¹⁸ Effective communication between surgeons, nurses, ancillary staff, and patients is not only a crucial element to improved patient outcomes, but it also leads to less medical litigation.¹⁹⁻²¹

A strong correlation exists between communication and patient outcomes.

Establishing a collaborative atmosphere is important since communication errors leading to medical mishaps are not simply failures to transmit information. Communication errors “are far more complex and relate to hierarchical differences, concerns

with upward influence, conflicting roles and role ambiguity, and interpersonal power and conflict.”^{17,22} Errors frequently originate from perceived limited channels of communication and hostile, critical environments. To overcome these barriers, surgeons and surgical trainees should learn to communicate in an open, universally understood manner and remain receptive to any team member’s concerns. A survey of physicians, nurses, and ancillary staff identified effective communication as a key element of a successful leader.²³ As leaders, surgeons and surgical trainees who facilitate an open, effective, collaborative style of communication reduce errors and enhance patient care. A prime example is that successful communication of daily goals of patient care from the team leader improves patient outcomes. In one recent study, the modest act of explicitly stating daily goals in a standardized fashion significantly reduced patient length of intensive care unit stay and increased resident and nurse understanding of goals of care.²⁴ Implementing standardized daily team briefings in the wards and preoperative units led to improvements in staff turnover rates, employee satisfaction, and prevention of wrong site surgery.²² In cardiac surgery, improving communication in the operating room and transition to the postanesthesia care unit was an area identified to decrease risk for adverse outcomes.²⁵ Behaviors associated with ineffective communication, including absence from the operating room when needed, playing loud music, making inappropriate comments, and talking to others in a raised voice or a condescending tone, were identified as patient hazards; conversely, behaviors associated with effective collaborative communication, such as time outs, repeat backs, callouts, and confirmations, resulted in improved patient outcomes.

One model to ensure open communication is through standardization of established protocols. A commonly accepted protocol is the “Time Out” that is now required in the modern operating room. During the Time Out protocol, all team members introduce themselves and state a body of critical information needed to safely complete the intended operation. This same standardization can be taught outside the operating room. Within the Kaiser system, certain phrases have been given a universal meaning: “I need you now” by members of the team is an understood level of urgency and generates a prompt physician response 100% of the time.²² As mentioned earlier, standardized forms can be useful tools in ensuring universally understood communication during sign-out. The beneficial effect of standardized communication further demonstrates how effective communication can improve patient care and is considered a vital leadership skill.

To Resolve Conflict. Great leaders are able to achieve their vision through their ability to resolve conflict. During the pursuit of any vision, numerous conflicts arise on a daily basis; numerous conflicts arise on a daily basis when surgeons and surgical trainees provide high-quality care. Therefore, the techniques for conflict resolution are essential for surgical leaders.

To properly use conflict resolution techniques, it is important for the surgeon and surgical trainee to always remain objective and seek personal flexibility and self-awareness. The gulf between self-perception and the perception of others can be profound; in a study of cooperation and collaboration among operating room staff, the quality of their own collaboration was rated at 80% by surgeons, yet was rated at only 48% by operating room nurses.²⁶ Systematic inclusion of modern conflict resolution methods that incorporate the views of all members of a multidisciplinary team help maintain objectivity. Reflection is

often overlooked in surgical residency training but is a critical component of learning conflict resolution skills. Introspection allows the surgeon to understand the impact of his or her actions and biases. Objectivity is the basis of effective conflict resolution, which can improve satisfaction among team members and help deliver optimal patient care.

Modern conflict resolution techniques are based on objectivity, willingness to listen, and pursuit of principle-based solutions.²⁷ For example, an effective style of conflict resolution is the utilization of the “abundance mentality” model, which attempts to achieve a solution that benefits all involved and is based on core values of the organization, as opposed to the utilization of the traditional fault-finding model, which identifies sides as right or wrong.²⁸ Application of the abundance mentality in surgery elevates the conflict above the affected parties and focuses on the higher unifying goal of improved patient care. Morbidity and mortality (M&M) conferences are managed in this style and have the purpose of practice improvement and improving overall quality of care within the system, as opposed to placing guilt or blame on the surgeon or surgical trainees for the complication being reviewed. The traditional style of command-and-control technique based on fear and intimidation is no longer welcome in any healthcare system and can lead to sanctions, lawsuits, and removal of hospital privileges or position of leadership.

Another intuitive method that can help surgical trainees learn to resolve conflict is the “history and physical” model of conflict resolution. This model is based on the seven steps of caring for a surgical patient that are well known to the surgical trainee.²⁹ (1) The “history” is the equivalent of gathering subjective information from involved parties with appropriate empathy and listening. (2) The “laboratory/studies” are the equivalent of collecting objective data to validate the subjective information. (3) A “differential diagnosis” is formed of possible root causes of the conflict. (4) The “assessment/plan” is developed in the best interest of all involved parties. The plan, including risks and benefits, is openly discussed in a compassionate style of communication. (5) “Preoperative preparation” includes the acquisition of appropriate consultations for clearances, consideration of equipment and supplies needed for implementation, and the “informed consent” from the involved parties. (6) The “operation” is the actual implementation of the agreed-upon plan, including a time-out. (7) “Postoperative care” involves communicating the operative outcome, regular postoperative follow-up, and the correction of any complications that arise. This seven-step method is an example of an objective, respectful method of conflict resolution. Practicing different styles of conflict resolution and effective communication in front of the entire group of surgical trainees attending the leadership training program is an effective means of teaching conflict resolution techniques.

Time Management

It is important for leaders to practice effective time management. Time is the most precious resource, as it cannot be bought, saved, or stored. Thus, management of time is essential for a productive and balanced life for those in the organization. The effective use of one’s time is best done through a formal time management program to improve one’s ability to lead by setting priorities and making choices to achieve goals. The efficient use of one’s time helps to improve both productivity and quality of life.

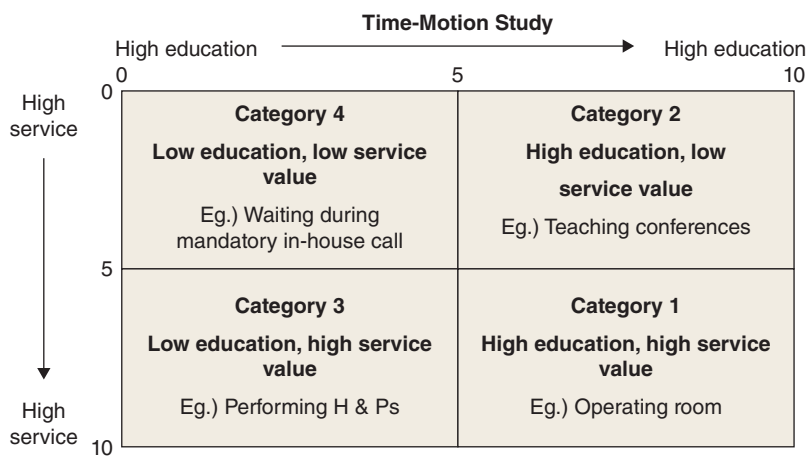


Figure 1-6. Surgery resident time-motion study. H & P = history and physical examination.

It is important for surgeons and surgical trainees to learn and use a formal time management program. There are ever-increasing demands placed on surgeons and surgical trainees to deliver the highest quality care in highly regulated environments. Furthermore, strict regulations on limitation of work hours demand surgical trainees learn patient care in a limited amount of time.³⁰ All told, these demands are enormously stressful and can lead to burnout, drug and alcohol abuse, and poor performance.³⁰ A time-motion study of general surgery trainees analyzed residents' self-reported time logs to determine resident time expenditure on educational/service-related activities (Fig. 1-6).³¹ Surprisingly, senior residents were noted to spend 13.5% of their time on low-service, low-educational value activities. This time, properly managed, could be used to either reduce work hours or improve educational efficiency in the context of new work hour restrictions. It is therefore critical that time be used wisely on effectively achieving one's goals.

Parkinson's law, proposed in 1955 by the U.K. political analyst and historian Cyril Northcote Parkinson, states that work expands to fill the time available for its completion, thus leading individuals to spend the majority of their time on insignificant tasks.³² Pareto's 80/20 principle states that 80% of goals are achieved by 20% of effort and that achieving the final 20% requires 80% of their effort. Therefore, proper planning of undertaking any goal needs to include an analysis of how much effort will be needed to complete the task.³² Formal time management programs help surgeons and surgical trainees better understand how their time is spent, enabling them to increase productivity and achieve a better balanced lifestyle.

Various time allocation techniques have been described.³² A frequently used basic technique is the "prioritized list," also known as the ABC technique. Individuals list and assign relative values to their tasks. The use of the lists and categories serves solely as a reminder, thus falling short of aiding the user in allocating time wisely. Another technique is the "time management matrix technique."²⁸ This technique plots activities on two axes: importance and urgency, yielding four quadrants (Fig. 1-7). Congruous with the Pareto's 80/20 principle and Parkinson's law, the time management matrix technique channels efforts into quadrant II (important but nonurgent) activities. The activities in this quadrant are high yield and include planning, creative activity, building relationships, and maintaining productivity. Too often, surgeons spend a majority of their time attending to

quadrant I (important and urgent) tasks. Quadrant I tasks include emergencies and unplanned or disorganized situations that require intensive and often inefficient effort. While most surgeons and surgical trainees have to deal with emergencies, they often develop the habit of inappropriately assigning activities into quadrant I; excess time spent on quadrant I tasks leads to stress or burnout for the surgeon and distracts from long-term goals. Efficient time management allows surgeons and surgical trainees to be proactive about shifting energy from quadrant I tasks to quadrant II, emphasizing preplanning and creativity over always attending to the most salient issue at hand, depending on the importance and not the urgency.

Finally, "the six areas of interest" is an alternative effective time management model that can help surgeons and surgical trainees achieve their goals, live a better balanced lifestyle, and improve the quality of their lives.³² The process begins by performing a time-motion study in which the activities of 6-hour increments of time over a routine week are chronicled. At the end of the week, the list of activities is analyzed to determine how the 168 hours in 1 week have been spent. The surgical trainee then selects six broad categories of areas of interest (i.e., family, clinical care, education, health, community service, hobbies, etc.), and sets a single activity goal in each category every day and monitors whether those goals are achieved. This technique is straightforward and improves one's quality of life by setting and achieving a balanced set of goals of personal interest, while eliminating time-wasting activities.

A formal time management program is essential for modern leadership. The practice and use of time management strategies can help surgeons and surgical trainees achieve and maintain their goals of excellent clinical care for their patients, while maintaining a more balanced lifestyle.

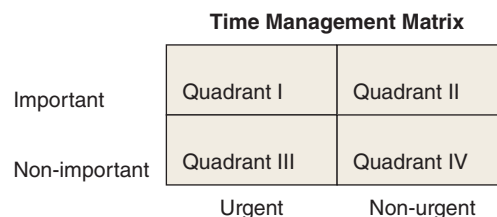


Figure 1-7. Time management. (From Covey S. *The Seven Habits of Highly Effective People*. New York: Simon & Schuster; 1989.)

LEADERSHIP STYLES

The principles of leadership can be practiced in a variety of styles. Just as there are many definitions of leadership, many classifications of styles exist as well. A landmark study by Daniel Goleman in *Harvard Business Review* identified six distinct leadership styles, based on different components of emotional intelligence.³³ Emotional intelligence is the ability to recognize, understand, and control the emotions in others and ourselves. By learning different styles, surgeons and trainees can recognize their own leadership style and the effect on the team dynamic. Furthermore, it teaches when the situation may demand change in style for the best outcome. The six leadership styles identified are *Coercive, Authoritative, Affiliative, Democratic, Pacesetter, and Coaching*.

The Coercive leader demands immediate compliance. This style reflects the command and control style that has historically dominated surgery. Excessive coercive leadership erodes team members' sense of responsibility, motivation, sense of participation in a shared vision, and ultimately, performance. However, it is effective in times of crisis to deliver clear, concise instruction. This style should be used sparingly and is best suited for emergencies.

The Authoritative leader embodies the phrase "Come with me," focusing on mobilizing the team toward a common, grand vision. This type of leader allows the team freedom to innovate, experiment, and devise its own means. Goleman's research indicates this style is often the most effective. These leaders display self-confidence, empathy, and proficiency in initiating new ideas and leading people in a new direction. This is best used when a shift in paradigm is needed.

The Affiliative leader creates harmony and builds emotional bonds. This requires employment of empathy, building relationships, and emphasis on communication. An affiliative leader frequently gives positive feedback. This style can allow poor performance to go uncorrected if too little constructive/critical advice is given. Affiliative leadership is most useful when motivating people during stressful circumstances or healing rifts in a team.

The Coaching style of leadership focuses on developing people for the future. Coaching is leadership through mentorship. The coach gives team members challenging tasks, counsels, encourages, and delegates. Unlike the affiliative leader who focuses on positive feedback, the coach helps people identify their weaknesses and improve their performance, and ties their work into their long-term career aspirations. This leadership style builds team capabilities by helping motivated learners improve. However, this style does not work well when team members are defiant and unwilling to change or learn, or if the leader lacks proficiency.

The Democratic leader forges consensus through participation. This leadership style listens to and values each member's input. It is not the best choice in an emergency situation, when time is limited, or when teammates cannot contribute informed guidance to the leader. It can also be exasperating if a clear vision does not arise from the collaborative process. This style is most appropriate when it is important to obtain team consensus, quell conflict, or create harmony.

The Pacesetter leader sets high standards for performance and exemplifies them. These leaders identify poor performers and demand more from them. However, unlike the coach, the pacesetter does not build the skills of those who are not keeping

up. Rather, a pacesetter will either take over the task himself or delegate the task to another team member. This leadership style works well when it is important to obtain high-quality results and there is a motivated, capable team. However, pacesetters can easily become micromanagers who have difficulty delegating tasks to team members, which leads to burn out on the part of the leader. Additionally, team members can feel overwhelmed and demoralized by the demands for excellence without an empathic counter balance.

Each of the above styles of leadership has strengths and weakness. Importantly, leaders who are the most successful do not rely only on one leadership style alone. They use several of them seamlessly depending on the situation and the team members at hand. Therefore, the more styles a leader has mastered, the better, with particular emphasis on the Authoritative, Affiliative, Democratic, and Coaching styles. Each leadership style is a tool that is ultimately employed to guide a team to realizing a vision or goal. Thus, leadership training programs should teach the proper use of all leadership styles while adhering to the principles of leadership.

FORMAL LEADERSHIP TRAINING PROGRAMS IN SURGERY

Since it has been shown that effective leadership can improve patient outcomes, leadership principles and skills should be taught to surgical trainees using formal leadership training programs. The importance of teaching leadership skills is reflected by the ACGME mandated core competencies (see Table 1-1). However, surgical trainees, most notably chief residents, find themselves in various leadership roles without ever having experienced formalized leadership training, which has been shown to result in a self-perceived lack of leadership ability.²³ When surveyed on 18 core leadership skills (Table 1-2), 92% of residents rated all 18 skills as important, but over half rated themselves as "minimally" or "not competent" in 10 out of 18 skills.² It has been documented that trainees are requesting leadership training and wish to close the gap between perceived need for training and the implementation of formal leadership training programs.³⁴⁻³⁷

A number of leadership workshops have been created. Extracurricular leadership programs have been designed mostly for physicians with an MBA or management background but have not been incorporated into the core residency training program.³⁸ Also, there are many institutions that have published experiences with leadership retreats or seminars for residents or young physicians.³⁹⁻⁴² The ACGME hosts multiple leadership skills workshops for chief residents, mostly targeted toward pediatricians, family practitioners, and psychiatrists.⁴³ Similarly, the American College of Surgeons leads an annual 3-day leadership conference focusing on leadership attributes, consensus development, team building, conflict resolution, and translation of leadership principles into clinical practice.⁴⁴ These programs were all received well by participants and represent a call for a formal leadership program for all surgical trainees.

An innovative leadership curriculum first implemented in 1999 taught general surgery trainees collaborative leadership skills, at a time when the traditional command-and-control leadership style predominated.⁴⁵ Surgical residents participated in 18-hour-long modules based on the leadership principles and skills listed in Table 1-2, taught by the surgical faculty.

Table 1-2

18 leadership training modules

SKILLS	IMPORTANCE MEAN SCORE	COMPETENCE MEAN SCORE
Academic program development	3.2	2.4*
Leadership training	3.8	2.3*
Leadership theory	3.2	2.1*
Effective communication	3.7	2.7*
Conflict resolution	3.8	3*
Management principles	3.7	2.7*
Negotiation	3.7	2.8*
Time management	4	2.8*
Private or academic practice, managed care	3.6	2*
Investment principles	3.5	2.2*
Ethics	3.6	3.2
Billing, coding, and compliance	3.5	1.7*
Program improvement	3	2*
Writing proposals	3.3	2.2*
Writing reports	3.4	2.4*
Public speaking	3.7	2.7*
Effective presentations	3.7	2.7*
Risk management	3.5	2.1*
Total	3.6	2.5*

Source: Reprinted with permission from Itani KMF, Liscum K, Brunicaudi FC. Physician leadership is a new mandate in surgical training. *Am J Surg*. 2004;187:328-331. © Copyright Elsevier.

* P<0.001 by Student t test between mean importance and mean competence scores.

A number of leadership techniques, including time management techniques and applied conflict resolution techniques described earlier, were designed and implemented as part of this leadership training program. Within 6 months of implementation, residents' self-perceived total commitment to the highest personal and professional standards, communication skills, visualization of clear missions of patient care, and leadership of others toward that mission increased significantly.⁴⁵ Remarkably, the positive impact of this leadership curriculum was significant when measured using tools, such as the Multifactor Leadership Questionnaire (MLQ), social skills inventory, personality inventory, and internal strength scorecard.^{2,37,45-47} The MLQ is a well-validated instrument that objectively quantifies leadership beliefs and self-perceived outcomes across medical and nonmedical disciplines. Based on the MLQ, surgical residents more often use a passive-avoidant style of leadership that emphasizes taking corrective action only after a problem is "significant and obvious."³⁷ This tool can also be used to track progress toward more effective, collaborative styles of leadership. These studies demonstrated the ability to measure leadership behavior of surgical trainees in a standardized, quantifiable format.^{2,37,45-47} Taken together, these studies support the concept that leadership skills can and should

be taught to surgical trainees, and there are many validated tools **8▶** to measure outcomes.

Mentoring

A formal leadership training program for surgical trainees should include mentoring. Mentoring is the active process by which an experienced, empathetic person guides another individual in the development and self-recognition of their own vision, learning, core competencies, and professional development. Halstead established the concept of a surgical mentor who directly provided the trainees with professional and technical guidance. Halstead's concept went beyond a simple preceptorship by emphasizing clinical decision making based on scientific evidence. His goal was to develop surgeons who would go on to become outstanding leaders and innovators in the field. Although surgery has changed dramatically since Halstead's era, mentorship remains crucial in surgical training. In addition to teaching technical skills, clinical judgment, and scientific inquiry, modern-day mentors must also model effective communication, empathy, humanism, and the prioritization of competing professional and personal activities.

The mentor must also be an experienced and trusted advisor committed to the success of the mentee. A greater level of trust and commitment distinguishes the mentor from the teacher. More than a teacher, a mentor is a coach. The goal of a teacher is to pass on a defined level of knowledge for each stage of a student's education. The underlying premise is a limited level of advancement for the student. The coach, on the other hand, has the sole purpose to make his or her student the best at their game with an unlimited level of advancement. Modern mentorship implies a partnership between the mentor and the mentee. Surgical residency program chairs and program directors must recruit and develop faculty "coaches" to mentor residents to optimize their potential. Emeritus Chair of University of California, Los Angeles Head and Neck Surgery, Dr. Paul Ward, said it best: "We strive to produce graduates of our residency program who are among those who change the way we think and practice . . ." Having more than 25 former residents become chairs of academic head and neck surgical programs, Dr. Ward embodied the role as a surgeon's coach. The responsibilities of an effective mentor are summarized by Baroness: "Mentoring, to be effective, requires of the mentor empathy, maturity, self-confidence, resourcefulness, and willingness to commit time and energy to another. The mentor must be able to offer guidance for a new and evolving professional life, to stimulate and challenge, to encourage self-realization, to foster growth, and to make more comprehensible the landscape in which the protégé stands."⁴⁸

One of the major goals of a mentor is to assess the aptitudes and abilities of the mentee with regard to the appropriateness of their vision for their surgical career. Proper selection of the appropriate mentor can bring to the mentee much needed wisdom, guidance, and resources and can expand the scope of their vision. In addition, the mentor can refine the leadership **9▶** skills taught to their mentees in formal training programs. Highly successful surgeons most often have had excellent surgical mentors. It is impressive to note that more than 50% of United States Nobel laureates have served under other Nobel laureates in the capacity of student, postdoctoral fellow, or junior collaborator.⁴⁹ In academic medicine, evidence-based studies have shown benefits to the mentees that include enhanced

research productivity, higher likelihood of obtaining research grants, and greater success in obtaining desired positions in practice or at academic institutions.⁵⁰ Mentoring provides benefits to the mentors themselves, including refinement of their own personal leadership skills and a strong sense of satisfaction and accomplishment.

Mentorship is essential to accomplish the successful development of surgical trainees and to help cultivate their vision. Therefore, formal leadership training programs that have a goal of training the future leaders in surgery should include mentoring.

CONCLUSION

Although there are several definitions of leadership and a variety of leadership styles, all end with the common goal of improving patient care in the modern era. All forms of leadership require a vision and willingness—the willingness to assume the responsibility to lead, continue learning, practice effective communication styles, and resolve conflict. Effective leadership can change surgical departments and improve patient care through innovation. A growing body of evidence suggests the mastery of leadership requires practice through intentional curriculum and reinforcement through mentorship.

Surgical leadership is bred through its training programs. Thus, innovation in surgical training programs is needed to enhance the development of leadership skills of surgical trainees, to prepare them for practice in modern healthcare systems, and to optimize patient care, as well as compliance with requirements set forth by regulatory institutions governing surgery and surgical education. A growing body of literature supports the value of effective leadership in improving patient care, productivity, and the work environment while it validates the ability to measure the impact of leadership training. Therefore, it is of paramount importance to teach modern leadership principles and skills to surgical trainees in order to create a new generation of surgeon leaders who will shape the modern era of surgery in the context of rapidly evolving science, technology, and systems of healthcare delivery.

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chapter 2

Systemic Response to Injury and Metabolic Support

Siobhan A. Corbett*

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OVERVIEW: INJURY-ASSOCIATED SYSTEMIC INFLAMMATORY RESPONSE

The inflammatory response to injury or infection occurs as a consequence of the local or systemic release of “pathogen-associated” or “damage-associated” molecules, which use similar signaling pathways to mobilize the necessary resources required for the restoration of homeostasis. Minor host insults result in a localized inflammatory response that is transient and in most cases beneficial. Major host insults, however, may lead to amplified reactions, resulting in systemic inflammation, remote organ damage, and multiple organ failure in as many as 30% of those who are severely injured. Recent data support

this idea and suggest that severely injured patients who are destined to die from their injuries differ from survivors only in the degree and duration of their dysregulated acute inflammatory response.^{1,2}

This topic is highly relevant because systemic inflammation is a central feature³ of both sepsis and severe trauma. Understanding the complex pathways that regulate local and systemic inflammation is necessary to develop therapies to intervene during overwhelming sepsis or after severe injury. Sepsis, defined by a systemic inflammatory response to infection, is a disease process with an incidence of over 900,000 cases per year. Further, trauma is the leading cause of mortality and morbidity for individuals under age 45.

*This chapter is dedicated to its previous author, Dr. Stephen Lowry, my mentor and friend.

Key Points

- 1▶ Endogenous **damage-associated molecular patterns (DAMPs)** are produced following tissue and cellular injury. These molecules interact with immune and nonimmune cell receptors to initiate a “sterile” systemic inflammatory response following severe traumatic injury.
- 2▶ In many cases, DAMP molecules are sensed by **pattern recognition receptors (PRRs)**, which are the same receptors that cells use to sense invading pathogens. This explains, in part, the similar clinical picture of systemic inflammation observed in injured and/or septic patients.
- 3▶ The central nervous system receives information with regard to injury-induced inflammation via soluble mediators as well as **direct neural projections** that transmit information to regulatory areas in the brain. The resulting neuroendocrine reflex plays an important modulatory role in the immune response.
- 4▶ Inflammatory signals activate key **cellular stress responses** (the oxidative stress response, the heat shock protein response, the unfolded protein response, autophagy, and programmed cell death), which serve to mobilize cellular defenses and resources in an attempt to restore homeostasis.
- 5▶ The cells, mediators, signaling mechanisms, and pathways that compose and regulate the systemic inflammatory response are **closely networked** and **tightly regulated** by transcriptional events as well as by epigenetic mechanisms, posttranslational modification, and microRNA synthesis.
- 6▶ Nutritional assessments, whether clinical or laboratory guided, and intervention should be considered at an early juncture in all surgical and critically ill patients.
- 7▶ Management of critically ill and injured patients is optimized with the use of evidence-based and algorithm-driven therapy.

In this chapter, we will review what is known about the soluble and cellular effectors of the injury-induced inflammatory response; how the signals are sensed, transduced, and modulated; and how their dysregulation is associated with immune suppression. We will also discuss how these events are monitored and regulated by the central nervous system. Finally, we will review how injury reprograms cellular metabolism, in an attempt to mobilize energy and structural stores to meet the challenge of restoring homeostasis.

THE DETECTION OF CELLULAR INJURY

The Detection of Injury is Mediated by Members of the Damage-Associated Molecular Pattern Family

Traumatic injury activates the innate immune system to produce a systemic inflammatory response in an attempt to limit damage and to restore homeostasis. It includes two general responses: (a) an acute proinflammatory response resulting from innate immune system recognition of ligands, and (b) an anti-inflammatory response that may serve to modulate the proinflammatory phase and direct a return to homeostasis (Fig. 2-1). This is accompanied by a suppression of adaptive immunity.⁴ Rather than occurring sequentially, recent data indicate that all three responses are simultaneously and rapidly induced following severe traumatic injury.²

The degree of the systemic inflammatory response following trauma is proportional to injury severity and is an independent predictor of subsequent organ dysfunction and resultant mortality. Recent work has provided insight into the mechanisms by which immune activation in this setting is triggered. The clinical features of the injury-mediated systemic inflammatory response, characterized by increased body temperature, heart rate, respirations, and white blood cell count, are similar to those observed with infection (Table 2-1). While significant efforts have been devoted to establishing a microbial etiology for this response, it is now widely accepted that systemic inflammation following trauma is sterile. Although the mechanisms for the sterile response are

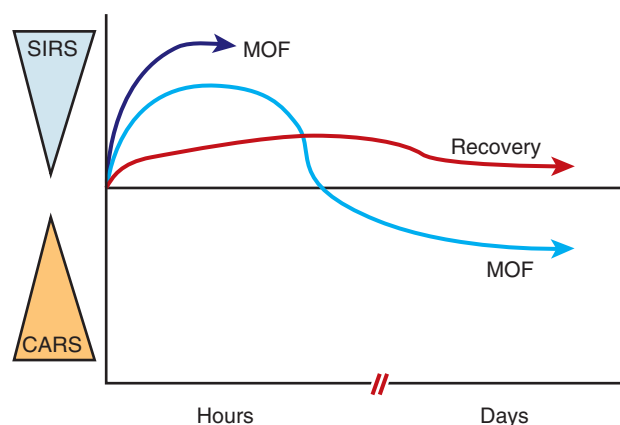


Figure 2-1. Schematic representation of the systemic inflammatory response syndrome (SIRS) after injury, followed by a period of convalescence mediated by the counterregulatory anti-inflammatory response syndrome (CARS). Severe inflammation may lead to acute multiple organ failure (MOF) and early death after injury (dark blue arrow). A lesser inflammatory response followed by excessive CARS may induce a prolonged immunosuppressed state that can also be deleterious to the host (light blue arrow). Normal recovery after injury requires a period of systemic inflammation followed by a return to homeostasis (red arrow). (Adapted with permission from Guirao X, Lowry SF. *Biologic control of injury and inflammation: Much more than too little or too late.* World J Surg. 1996;20:437. With kind permission from Springer Science + Business Media.)

less well understood, it is likely to result from endogenous molecules that are produced as a consequence of tissue damage or cellular stress, as may occur with hemorrhagic shock and resuscitation.⁵ Termed **alarmins or damage-associated molecular patterns (DAMPs)**, these effectors, along with the **pathogen-associated molecular patterns (PAMPs)**, interact with specific cell receptors that are located both on the cell surface and intracellularly.⁶ The best described of these receptors are members of the toll-like receptor family.

Table 2-1

Clinical spectrum of infection and systemic inflammatory response syndrome (SIRS)

TERM	DEFINITION
Infection	Identifiable source of microbial insult
SIRS	Two or more of following criteria are met: Temperature $\geq 38^{\circ}\text{C}$ (100.4°F) or $\leq 36^{\circ}\text{C}$ (96.8°F) Heart rate ≥ 90 beats per minute Respiratory rate ≥ 20 breaths per minute or $\text{Paco}_2 \leq 32$ mmHg or mechanical ventilation White blood cell count $\geq 12,000/\mu\text{L}$ or $\leq 4000/\mu\text{L}$ or $\geq 10\%$ band forms
Sepsis	Identifiable source of infection + SIRS
Severe sepsis	Sepsis + organ dysfunction
Septic shock	Sepsis + cardiovascular collapse (requiring vasopressor support)

Paco_2 = partial pressure of arterial carbon dioxide.

Trauma DAMPs are structurally diverse endogenous molecules that are immunologically active. Table 2-2 includes a partial list of DAMPs that are released either passively from necrotic/damaged cells or actively from physiologically “stressed” cells by upregulation or overexpression. Once they are outside the cell, DAMPs promote the activation of innate immune cells, as well as the recruitment and activation of antigen-presenting cells, which are engaged in host defense.⁷ The best-characterized DAMP with significant preclinical evidence for its release after trauma and with a direct link to the systemic inflammatory response is high-mobility group protein B1 (HMGB1). Additional evidence for the role of DAMP molecules in postinjury inflammation, including mitochondrial proteins and DNA, as well as extracellular matrix molecules, is also presented.

Table 2-2

Damage-associated molecular patterns (DAMPs) and their receptors

DAMP MOLECULE	PUTATIVE RECEPTOR(S)
HMGB1	TLRs (2,4,9), RAGE
Heat shock proteins	TLR2, TLR4, CD40, CD14
S100 protein	RAGE
Mitochondrial DNA	TLR9
Hyaluronan	TLR2, TLR4, CD44
Biglycan	TLR2 and TLR4
Formyl peptides (mitochondrial)	Formyl peptide receptor 1
IL-1 α	IL-1 receptor

HMGB1 = high-mobility group protein B1; IL = interleukin; RAGE = receptor for advanced glycosylation end products; TLK = toll-like receptor.

High-Mobility Group Protein B1. The best-characterized DAMP in the context of the injury-associated inflammatory response is HMGB1 protein, which is rapidly released into the circulation within 30 minutes following trauma. HMGB1 is highly evolutionarily conserved across species. It was first described as a constitutively expressed, nonhistone chromosomal protein that participated in a variety of nuclear events, including DNA repair and transcription. HMGB1 was also detected in the cytosol and extracellular fluids at low levels, although its function outside the cell was not clear. Subsequent studies have proven, however, that HMGB1 is actively secreted from immune-competent cells stimulated by PAMPs (e.g., endotoxin) or by inflammatory cytokines (e.g., tumor necrosis factor and interleukin-1). This process occurs outside the classic secretory pathway via a mechanism that is independent of endoplasmic reticulum and the Golgi complex. Moreover, recent data indicate that HMGB1 release can be regulated by the inflammasome.⁸ Stressed nonimmune cells such as endothelial cells and platelet also actively secrete HMGB1. Finally, passive release of HMGB1 can occur following cell death, whether it is programmed or uncontrolled (necrosis).

Once outside the cell, HMGB1 interacts with its putative receptors either alone or in concert with pathogenic molecules to activate the immune response, and in this way, functions as a proinflammatory cytokine. HMGB1 has been shown to signal via the toll-like receptors (TLR2, TLR4, TLR9), the receptor for advanced glycosylation end products (RAGE), CD24, and others. The activation of TLRs mainly occurs in myeloid cells, whereas RAGE is thought to be the receptor target in endothelial and somatic cells. The diverse proinflammatory biologic responses that result from HMGB1 signaling include: (a) the release of cytokines and chemokines from macrophages/monocytes and dendritic cells; (b) neutrophil activation and chemotaxis; (c) alterations in epithelial barrier function, including increased permeability; and (d) increased procoagulant activity on platelet surfaces, among others.⁹ In particular, HMGB1 binding to TLR4 triggers the proinflammatory cytokine release that mediates “sickness behavior.” This effect is dependent on the highly conserved domain structure of HMGB1 that can be recapitulated by a synthetic 20-amino acid peptide containing a critical cysteine residue at position 106.¹⁰

Recent data have explored the role of this cysteine residue, as well as two others that are highly conserved, in the biologic function of HMGB1. They demonstrate that the redox state of the three residues regulates the receptor binding ability of HMGB1 to influence its activity, including cytokine production. For example, a thiol at C106 is required for HMGB1 to promote macrophage tumor necrosis factor (TNF) release. In addition, a disulfide bond between C23 and C45 is also required for cytokine release because reduction of the disulfide linkage or further oxidation will reduce the ability of HMGB1 to function as a cytokine. Therefore, if all three cysteine residues are in reduced form, HMGB1 lacks the ability to bind and signal through TLR4, but gains the capacity to bind to CXCL12 to activate CXCR4 and serve as a chemotactic mediator. Importantly, shifts between the redox states have been demonstrated and indicate that redox state dynamics are important regulators of HMGB1.¹¹

Importantly, HMGB1 levels in human subjects following injury correlate with the Injury Severity Score, complement activation, and an increase in circulating inflammatory mediators such as TNF.¹² Unchecked, excessive HMGB1 has the capacity

to promote a self-injurious innate immune response. In fact, exogenous administration of HMGB1 to normal animals produces fever, weight loss, epithelial barrier dysfunction, and even death.

A Role for Mitochondrial DAMPs in the Injury-Mediated Inflammatory Response. Mitochondrial proteins and/or DNA can act as DAMPs by triggering an inflammatory response to necrosis and cellular stress. Specifically, the release of mitochondrial DNA (mtDNA) and formyl peptides from damaged or dysfunctional mitochondria has been implicated in activation of the macrophage **inflammasome**, a cytosolic signaling complex that responds to cellular stress. In support of this idea, plasma mtDNA has been shown to be thousands of times higher in both trauma patients and patients undergoing femoral fracture repair when compared to normal volunteers. Further, direct injection of mitochondria lysates in an animal model caused remote organ damage, including liver and lung inflammation.¹³ These data suggest that with stress or tissue injury, mtDNA and peptides are released from damaged mitochondria where they can contribute to a sterile inflammatory response. From an evolutionary perspective, given that eukaryotic mitochondria derive from bacterial origin, it would make sense that they retain bacterial features capable of eliciting a strong response that is typically associated with a pathogen trigger. For example, mtDNA is circular and contains hypomethylated CpG motifs that resemble bacterial CpG DNA. It is thus capable of producing formylated peptides, which potently induce an inflammatory phenotype in neutrophils, by increasing chemotaxis, oxidative burst, and cytokine secretion. In addition, the mitochondrial transcription factor A (TFAM), a highly abundant mitochondrial protein, is functionally and structurally homologous to HMGB1. It has also been shown to be released in high amounts from damaged cells where it acts in conjunction with mtDNA to activate TLR9 signaling.¹⁴

Extracellular Matrix Molecules Act as DAMPs. Recent work has explored the role of extracellular matrix (ECM) proteins in the TLR-mediated inflammatory response that follows tissue injury. These molecules, which are sequestered under normal conditions, can be released in a soluble form with proteolytic digestion of the ECM. Proteoglycans, glycosaminoglycans, and glycoproteins such as fibronectin have all been implicated as key players in the DAMP/TLR interaction. Proteoglycans, in particular, have also been shown to activate the intracellular inflammasomes that trigger sterile inflammation. These molecules, which consist of a protein core with one or more covalently attached glycosaminoglycan chains, can be membrane-bound, secreted, or proteolytically cleaved and shed from the cell surface.

Biglycan is one of the first proteoglycans to be described as a TLR ligand.¹⁵ It consists of a protein core containing leucine-rich repeat regions, with two glycosaminoglycan (GAG) side chains (chondroitin sulfate or dermatan sulfate). Although biglycan typically exists in a matrix-bound form, with tissue injury, it is released from the ECM in a soluble form where it interacts with TLR2 or TLR4 to generate an immediate inflammatory response.

Various proinflammatory cytokines and chemokines, including TNF- α and interleukin (IL)-1 β , are downstream effector molecules of biglycan/TLR2/4 signaling. Among these, the mechanism of biglycan-mediated autonomous

synthesis and secretion of mature IL-1 β is unique. Usually, release of mature IL-1 β from the cell requires two signals, one which is needed to initiate synthesis (TLR2/4-mediated) and the other to process pro-IL-1 β to its mature form (inflammasome-mediated). How is it possible for biglycan to provide both signals? Current evidence indicates that when soluble biglycan binds to the TLR, it simultaneously serves as a ligand for a purinergic receptor, which facilitates the inflammasome activation required for IL-1 β processing.¹⁶ These data support the idea that DAMP-mediated signals can initiate a robust inflammatory response.

DAMPs Are Ligands for Pattern Recognition Receptors

The inflammatory response that occurs following traumatic injury is similar to that observed with pathogen exposure.

▶ Not surprising, surface and cytoplasmic receptors that mediate the innate immune response to microbial infection have been implicated in the activation of sterile inflammation. In support of this idea, genes have been identified that are dysregulated acutely both in response to a microbial ligand administered to human volunteers and in response to traumatic injury in a large patient population.¹⁷ The classes of receptors that are important for sensing damaged cells and cell debris are part of the larger group of germline encoded **pattern recognition receptors** (PRRs). The best-described ligands for these receptors are microbial components, the PAMPs. The PRRs of the innate immune system fall into at least four distinct classes: TLRs, calcium-dependent (C-type) lectin receptors (CLRs), retinoic acid-inducible gene (RIG)-I-like receptors (RLRs), and the nucleotide-binding domain, leucine-rich repeat-containing (NBD-LRR) proteins (NLRs; also nucleotide-binding and oligomerization domain [NOD]-like receptors). Following receptor ligation, intracellular signaling modulates transcriptional and posttranslational events necessary for host defense by coordinating the synthesis and release of cytokines and chemokines to either initiate or suppress the inflammatory response. The best described of these, the TLRs, NLRs, and CLRs, are discussed in the following sections.

Toll-Like Receptors. The TLRs are evolutionarily conserved type 1 transmembrane proteins that are the best-characterized PRRs in mammalian cells. They were first identified in *Drosophila*, where a mutation in the *Toll* gene led to its identification as a key component in their immune defense against fungal infection. The first human TLR, TLR4, was identified shortly thereafter. Now, more than 10 human TLR family members have been identified, with distinct ligands that include lipid, carbohydrate, peptide, and nucleic acid components of various pathogens. TLRs are expressed on both immune and nonimmune cells. At first, the expression of TLR was thought to be isolated to professional antigen-presenting cells such as dendritic cells and macrophages. However, mRNA for TLR family members have been detected in most cells of myeloid lineage, as well as natural killer (NK) cells.¹⁸ In addition, activation of T cells increases their TLR expression and induces their survival and clonal expansion. Direct engagement of TLR in T-regulatory (Treg) cells promotes their expansion and reprograms them to differentiate into T helper cells, which in turn provides help to effector cells. In addition, B cells express a distinct subset of the TLR family that determines their ability to respond to DAMPs; however, the significance of restricted TLR expression in these cells is not yet clear.

All TLRs consist of an extracellular domain, characterized by multiple leucine-rich repeats (LRRs), and a carboxy-terminal, intracellular toll/IL-1 receptor (TIR) domain. The LRR domains recognize bacterial and viral PAMPs in the extracellular environment (TLR1, TLR2, TLR4, TLR5, TLR6, and TLR11) or in the endolysosomes (TLR3, TLR7, TLR8, TLR9, and TLR10). Although the role of TLRs in sepsis has been well described, more recent data indicate that a subset of the TLRs, TLR4 in particular, also recognizes DAMPs released from injured cells and tissues.¹⁹ Signal transduction occurs with receptor dimerization and recruitment of cytoplasmic adaptor proteins. These adaptor molecules initiate and amplify downstream signals, resulting in the activation of transcription. The transcription factors, which include nuclear factor- κ B (NF- κ B), activator protein (AP)-1, and interferon regulatory factor (IRF), bind to regulatory elements in promoters and/or enhancers of target genes leading to the upregulation of a large cohort of genes that include interferon (IFN)- α and IFN- β , nitric oxide synthase 2 (NOS2A), and TNF, which play critical roles in initiating innate immune responses to cellular injury and stress. Given the importance of TLR triggering of the innate immune response to immune homeostasis, it is no surprise that the process is tightly regulated. TLR expression is significantly increased following blunt traumatic injury. Further, TLR signaling is controlled at multiple levels, both posttranscriptionally via ubiquitination, phosphorylation, and microRNA actions that affect mRNA stability, as well as by the localization of the TLRs and their signaling complexes within the cell.

Nucleotide-Binding Oligomerization Domain-Like Receptor Family. The NLRs are a large family of proteins composed of intracellular PRRs that sense both endogenous (DAMPs) and exogenous (PAMPs) molecules to trigger innate immune activation. The best characterized of the NLRs is the NLR family pyrin domain-containing 3 (NLRP3), which is highly expressed in peripheral blood leukocytes. It forms the key “sensing” component of the larger, multiprotein **inflammasome** complex, which is composed of NLRP3; the adapter protein apoptosis-associated speck-like protein containing a CARD (ASC); and the effector protein, caspase 1.²⁰ In the cytoplasm, the receptor resides in an inactive form due to an internal interaction between two adjacent and highly conserved domains. In conjunction with a priming event, such as mitochondrial stress, phagocytosed DAMPs can be sensed by NLRP3, resulting in the removal of the self-repression. The protein can then oligomerize and recruit other complex members. The net result is the autoactivation of pro-caspase 1 to **caspase 1**. The NLRP3 inflammasome plays a central role in immune regulation by initiating the caspase 1-dependent processing and secretion of the proinflammatory cytokines IL-1 β and IL-18. In fact, NLRP3 is the key protein in the mechanism by which IL-1 β production is regulated in macrophages. NLRP3 inflammasome activity is tightly regulated by cell-cell interactions, cellular ion flux, and oxidative stress in order to maintain a balanced immune response to danger signals.

While the role of the NLRP3 inflammasome in the sterile inflammatory response following trauma has not been well described, recent evidence suggests that genetic variations in the *NLRP3* gene might affect the magnitude of immune inflammatory responses following trauma. Single nucleotide polymorphisms within the *NLRP3* gene were found to be associated with increased risk of sepsis and multiple organ dysfunction syndrome in patients with major trauma.²¹ In an animal model of burn injury, early

inflammasome activation has been detected in a variety of immune cells (NK cells, CD4/CD8 T cells, and B cells), as determined by the assessment of caspase 1 cleavage by flow cytometry.²² Further, inhibition of caspase 1 activity in vivo results in increased burn mortality, suggesting that inflammasome activation may play an unanticipated protective role in the host response to injury that may be linked to increased production of specific cytokines. In addition to the NLRP3 inflammasome, there are numerous other NLRP sensors that are capable of detecting a diverse range of molecular targets. Among them are those endogenous molecules that are released as a consequence of tissue injury and cellular stress (hypoxia/hypoperfusion).

C-Type Lectin Receptors. Macrophages and dendritic cells possess receptors that detect molecules released from damaged or dying cells in order to retrieve and process antigens from cell corpses for T-cell presentation. A key family of receptors that directs this process is the CLR family that includes the selectin and the mannose receptor families and that binds carbohydrates in a calcium-dependent fashion. Best described for their sensing of PAMPs, particularly fungal antigens, the CLRs can also act to promote the endocytosis and clearance of cell corpses. More recent work has demonstrated, however, that a subset of CLR receptors such as dendritic cell-NK lectin group receptor-1 (DNGR-1) and macrophage-inducible C-type lectin receptor (Mincle) recognize DAMPs of intracellular origin, such as F-actin and the ribonucleoprotein SAP-130.²³ Ligation and activation of Mincle promotes its interaction with an Fc γ receptor, which contains immunoreceptor tyrosine-based activation motifs. This leads to proinflammatory cytokine, chemokine, and nitric oxide production, in addition to neutrophil recruitment. In this way, Mincle may contribute to local inflammation at sites of tissue injury.

Soluble Pattern Recognition Molecules: The Pentraxins. Soluble pattern recognition molecules (PRMs) are a molecularly diverse group of molecules that share a conserved mode of action that is defined by complement activation, agglutination and neutralization, and opsonization. The best described of the PRMs are the **pentraxins**. PRMs can be synthesized at sites of injury and inflammation by macrophages and dendritic cells, while neutrophils can store PRMs and can release them rapidly following activation. In addition, epithelial tissues (the liver in particular) serve as a reservoir source for systemic mass release. The short pentraxin, **C-reactive protein (CRP)**, was the first PRM to be identified. Serum amyloid protein (SAP), which has 51% sequence similarity to human CRP, also contains the pentraxin molecular signature. CRP and SAP plasma levels are low (≤ 3 mg/L) under normal circumstances. However, CRP is synthesized by the liver in response to IL-6, increasing serum levels more than a 1000-fold. Thus, CRP is considered part of the **acute-phase protein response** in humans. For this reason, CRP has been studied as a marker of the proinflammatory response in many clinical settings, including appendicitis, vasculitis, and ulcerative colitis. CRP and SAP are ancient immune molecules that share many functional properties with antibodies: they bind bacterial polysaccharides, ECM components, apoptotic cells, and nuclear materials, as well as all three classes of Fc γ receptors (Fc γ R). Both molecules also participate in the activation and regulation of complement pathways. In this way, short pentraxins can link immune cells to the complement system.²⁴

Finally, significant data support a role for pentraxin 3 (PTX3), a long pentraxin family member, in the “sterile”

inflammatory response associated with cellular stress. While CRP is produced solely in the liver, PTX3 is produced by various cells in peripheral tissues, including immune cells. PTX3 plasma concentrations increase rapidly in various inflammatory conditions, including sepsis. Further, in a recent prospective study of polytraumatized patients, serum PTX3 concentrations were highly elevated, peaking at 24 hours. In addition, PTX3 concentrations at admission were associated with injury severity, whereas higher PTX3 serum concentrations 24 hours after admission correlated with lower probability for survival.²⁵

Pattern Recognition Receptor Signaling: Toll-Like Receptors and the Inflammasome

As noted earlier, members of the TLR family respond to endogenous molecules released from damaged or stressed cells. In animal models, activation of TLRs in the absence of bacterial pathogens correlates with the development of critical illness including “sterile inflammation.” What we know about TLR signaling events has largely been derived from the TLR-mediated response to bacterial pathogens. However, it is likely that the intracellular adaptors required for signal transmission by TLRs in response to exogenous ligands are conserved and used for “damage” sensing of endogenous (“self”) ligands as well. The intracellular domain structure of TLRs is highly conserved and is characterized by a cytoplasmic toll/IL-1R homology (TIR) domain. Binding of ligand to the receptor results in a receptor dimer, either a homodimer (e.g., TLR4/TLR4) or heterodimer (e.g., TLR2/TLR1), which recruits a number of adaptor proteins to the TIR domains, through TIR-TIR interaction.²⁶ With one exception (TLR3), the universal adaptor protein central to the TLR signaling complex is myeloid differentiation factor 88 (MyD88), a member of the IL-1 receptor subfamily. MyD88 works through the recruitment of a second TIR-containing adaptor, MyD88 adaptor-like protein (Mal), in the context of TLR4 and TLR2 signaling, which serves as a bridge between MyD88 and activated TLRs to initiate signal transduction. It is interesting that Mal’s adaptor function requires cleavage of the carboxy-terminal portion of the protein by **caspase 1**, a key effector of the inflammasome.²⁷ This finding suggests an important synergy between TLRs and NLRs that may potentiate TLR-mediated signaling. There are three other TIR domain-containing adaptor proteins that are also important to TLR-signaling events; these are TIR-domain-containing adapter-inducing INF- β (TRIF), TRIF-related adaptor molecule (TRAM), and sterile α - (SAM) and HEAT/armadillo (ARM) motif-containing protein (SARM). Two of these, TRIF and TRAM, are involved in the *MyD88-independent* signaling pathways, which are activated by TLR3 and TLR4.

Signaling through the MyD88-dependent pathway results in the activation of numerous cytoplasmic protein kinases including IL-1 receptor–associated kinases (IRAK-1 and IRAK-4), resulting in an interaction with TNF receptor–associated factor 6 (TRAF6). TRAF6, an E3 ubiquitin ligase, forms a complex with two other proteins, which together activate the complex that subsequently phosphorylates I κ B kinase (IKK)- β and the MAP kinases (MAPKs). Ultimately, the phosphorylation of I κ B by the IKK complex and NEMO (NF- κ B essential modulator) leads to its degradation, which frees NF- κ B and allows its translocation to the nucleus and the transcription of **NF- κ B target genes**. Simultaneously, MAPK activation is critical for activation of the activator protein-1 (AP-1) transcription factor, and thus production of **inflammatory cytokines**.

The MyD88-independent pathway acts through TRIF to activate NF- κ B, similar to the MyD88-dependent pathway. However, TRIF can also recruit other signaling molecules to phosphorylate interferon-regulatory factor 3 (IRF3), which induces expression of type I IFN genes.²⁶

Signaling from the Inflammasome. As discussed earlier, activation and assembly of the inflammasome in response to DAMP sensing result in the cleavage of pro-caspase 1 into two products. This event is pivotal to all known inflammasome signaling pathways. The caspase 1 products assemble to form the **IL-1 converting enzyme (ICE)**, which cleaves the IL-1 cytokines, IL-1 β , IL-18, and IL-33. This final step is required for activation and secretion of the cytokines from the cell.²⁰ IL-1 β and IL-18 are potent proinflammatory cytokines that promote key immune responses that are essential to host defense. Thus, the synthesis, processing, and secretion of these cytokines are tightly regulated, as successful cytokine release requires a two-step process. The first signal, which is typically TLR-mediated, initiates the synthesis and storage of the inactive cytokine precursors in the cytoplasm. The second signal, which is inflammasome-mediated, initiates proteolytic cleavage of the procytokine, which is a requirement for its activation and secretion from the cell. Of further interest, evidence has demonstrated that both IL-1 β and IL-18 lack a signal sequence, which is usually necessary for those proteins that are destined for cellular export. These signal peptides target proteins to the endoplasmic reticulum (ER) and to the Golgi complex, where they are packaged for secretion from the cell through the classical secretory pathway. More than 20 proteins in addition to IL-1 β and IL-18 undergo **unconventional protein secretion** independent of the ER and Golgi complex.²⁸ The list includes signaling molecules involved in inflammatory, cell survival, and repair responses, such as HMGB1, IL-1 α , galectins 1 and 3, and FGF2. Currently, the mechanisms responsible for unconventional protein secretion are not understood; however, the process is also evident in yeast under conditions of cellular stress. It makes evolutionary sense that a mechanism for rapid secretion of stored proteins essential to the stress response is highly conserved.

CENTRAL NERVOUS SYSTEM REGULATION OF INFLAMMATION IN RESPONSE TO INJURY

The central nervous system (CNS) communicates with the body through ordered systems of sensory and motor neurons, which receive and integrate information to generate a coordinated response. Rather than being an immune-privileged organ, recent work indicates that the CNS receives information with regard to injury-induced inflammation both via soluble mediators as well as direct neural projections that transmit information

3► to regulatory areas in the brain (Fig. 2-2). How does the CNS sense inflammation? DAMPs and inflammatory molecules convey stimulatory signals to the CNS via multiple routes. For example, soluble inflammatory signaling molecules from the periphery can reach neurons and glial cells directly through the fenestrated endothelium of the circumventricular organs (CVO) or via a leaky blood brain barrier in pathologic settings such as may occur following a traumatic brain injury.²⁹ In addition, inflammatory stimuli can interact with receptors located on the brain endothelial cells to generate a variety of proinflammatory mediators (cytokines, chemokines, adhesion molecules, proteins of the complement system, and immune receptors) that directly impact the brain parenchyma. Not surprising, this

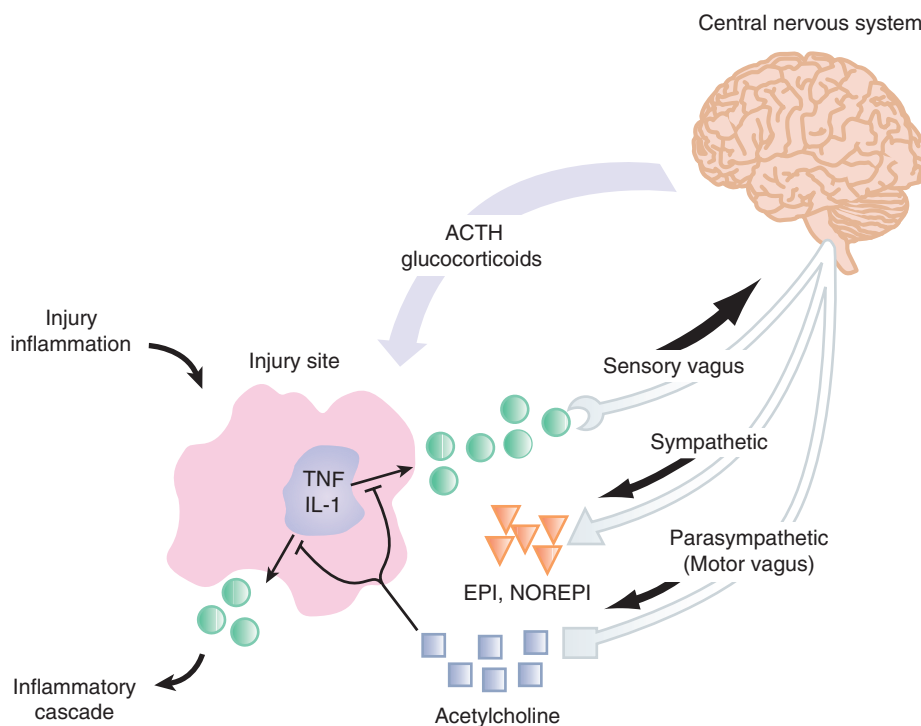


Figure 2-2. Neural circuit relaying messages of localized injury to the brain (nucleus tractus solitarius). The brain follows with a hormone release (adrenocorticotrophic hormone [ACTH], glucocorticoids) into the systemic circulation and by sympathetic response. The vagal response rapidly induces acetylcholine release directed at the site of injury to curtail the inflammatory response elicited by the activated immunocytes. This vagal response occurs in real time and is site specific. EPI = epinephrine; IL-1 = interleukin-1; NOREPI = norepinephrine; TNF = tumor necrosis factor. (Adapted and re-created with permission from Macmillan Publishers Ltd. Tracey KJ. *The inflammatory reflex*. *Nature*. 2002;420:853. Copyright © 2002.)

response is countered by potent anti-inflammatory signaling, a portion of which is provided by the hypothalamic-pituitary-adrenal (HPA) axis and the release of systemic glucocorticoids. Inflammatory stimuli in the CNS result in behavioral changes, such as increased sleep, lethargy, reduced appetite, and the most common feature of infection, fever.

Information regarding peripheral inflammation and tissue damage can also be signaled to the brain via afferent neural fibers, particularly those of the vagus nerve.³⁰ These afferent fibers can interconnect with neurons that project to the hypothalamus to modulate the HPA axis. In addition, afferent vagal nerve impulses modulate cells in the brain stem, at the dorsal motor nucleus of the vagus, from which efferent preganglionic parasympathetic impulses originate. Axons from these cells, which comprise the visceromotor component of the vagus nerve, form an “inflammatory reflex” that feeds back to the periphery to regulate inflammatory signaling events.³¹ Although the mechanisms by which cholinergic signals from the CNS regulate immune cells in the periphery are incompletely understood, recent evidence has provided some mechanistic insight. The first line of evidence to support this idea is the observation that vagal stimulation reduces proinflammatory cytokine production from the spleen in several experimental models systems.³² This effect is dependent on both the vagal efferent signals and, in part, splenic catecholaminergic nerve fibers that originate in the celiac plexus and that terminate in a T-cell-rich area of the spleen. Interestingly, these signals propagated by adrenergic nerves result in measurable increases in acetylcholine (ACh) levels in the spleen. In addition, the resident immune cells in the spleen require the expression of cholinergic receptors,

specifically $\alpha 7$ nicotinic acetylcholine receptors ($\alpha 7$ nAChR), for the suppression of cytokine synthesis.³³ How is this effect mediated? The apparent source of ACh is choline-acetyltransferase-expressing T cells, which compose 2% to 3% of CD4⁺ T cells in the spleen and are capable of ACh production. Data also indicate that the vagus nerve may regulate inflammation in tissues that it directly innervates.

Neuroendocrine Response to Injury

Traumatic injury results in complex neuroendocrine signaling from the brain that serves to enhance immune defense and rapidly mobilize substrates necessary to meet essential energy and structural needs. The two principle neuroendocrine pathways that orchestrate the host response are the **hypothalamic-pituitary-adrenal (HPA) axis**, which results in the release of glucocorticoid hormones, and the **sympathetic nervous system**, which results in release of the catecholamines, epinephrine, and norepinephrine. Virtually every hormone of the HPA axis influences the physiologic response to injury and stress (Table 2-3), but some with direct influence on the inflammatory response or immediate clinical impact are highlighted here, including growth hormone (GH), macrophage inhibitory factor (MIF), aldosterone, and insulin.

The Hypothalamic-Pituitary-Adrenal Axis. One of the main mechanisms by which the brain responds to injury-associated stress is through activation of the HPA axis. Following injury, corticotrophin-releasing hormone (CRH) is secreted from the paraventricular nucleus (PVN) of the hypothalamus. This action is mediated in part by circulating cytokines produced as

Table 2-3

Hormones regulated by the hypothalamus, pituitary, and autonomic system

Hypothalamic Regulation

- Corticotropin-releasing hormone
- Thyrotropin-releasing hormone
- Growth hormone–releasing hormone
- Luteinizing hormone–releasing hormone

Anterior Pituitary Regulation

- Adrenocorticotropic hormone
- Cortisol
- Thyroid-stimulating hormone
- Thyroxine
- Triiodothyronine
- Growth hormone
- Gonadotrophins
- Sex hormones
- Insulin-like growth factor
- Somatostatin
- Prolactin
- Endorphins

Posterior Pituitary Regulation

- Vasopressin
- Oxytocin

Autonomic System

- Norepinephrine
- Epinephrine
- Aldosterone

Renin-Angiotensin System

- Insulin
- Glucagon
- Enkephalins

a result of the innate immune response to injury. These include TNF- α , IL-1 β , IL-6, and the type I IFNs (IFN- α/β). Cytokines that are produced as a result of the adaptive immune response (IL-2 and IFN- γ) are also capable of increasing cortisol release. Direct neural input via afferent vagal fibers that interconnect with neurons projecting to the hypothalamus can also trigger CRH release. CRH acts on the anterior pituitary to stimulate the secretion of adrenocorticotropin hormone (ACTH) into the systemic circulation. Interestingly, the cytokines that act on the hypothalamus are also capable of stimulating ACTH release from the anterior pituitary so that marked elevations in ACTH and in cortisol can occur that are proportional in magnitude to the injury severity. Additionally, pain, anxiety, vasopressin, angiotensin II, cholecystokinin, vasoactive intestinal peptide, and catecholamines all contribute to ACTH release in the injured patient.

ACTH acts on the zona fasciculata of the adrenal glands to synthesize and secrete glucocorticoids (Fig. 2-3). Cortisol is the major glucocorticoid in humans and is essential for survival during significant physiologic stress. The resulting increase in cortisol levels following trauma have several important anti-inflammatory actions.

Cortisol elicits its many actions through a cytosolic receptor, the glucocorticoid receptor (GR). Because it is lipid soluble, cortisol can diffuse through the plasma membrane to interact with its receptor, which is sequestered in the cytoplasm in a complex with heat shock proteins (Fig. 2-4). Upon ligand binding, the GR is activated and can employ a number of mechanisms to modulate proinflammatory gene transcription and signaling events, with a “net” anti-inflammatory effect.³⁴ For example, the activated GR complex can interact with transcription factors to sequester them in the cytoplasm, promote their degradation, or inhibit them through other mechanisms. Affected target genes include proinflammatory cytokines, growth factors, adhesion molecules, and nitric oxide. In addition, glucocorticoids can negatively affect the access of the transcription factor, NF- κ B,

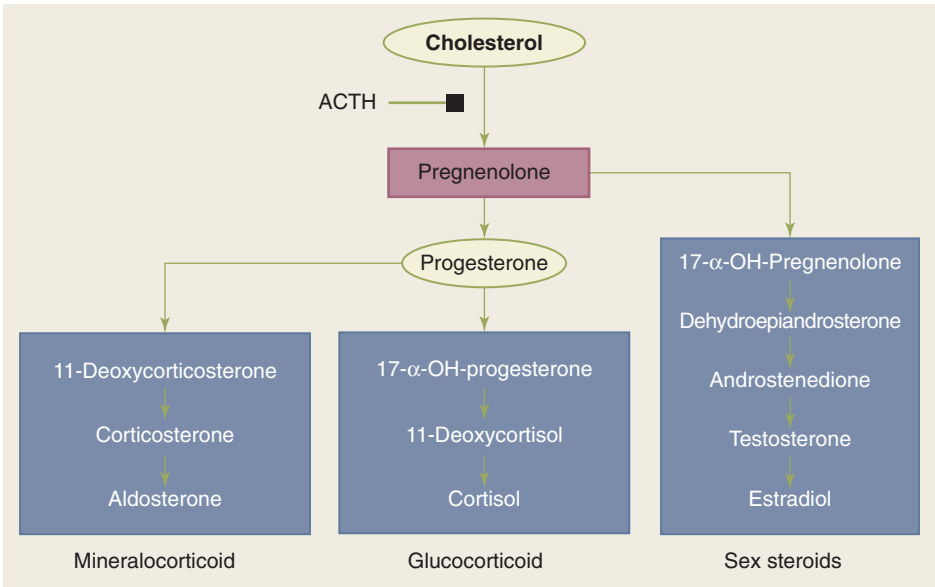


Figure 2-3. Steroid synthesis from cholesterol. Adrenocorticotropin hormone (ACTH) is a principal regulator of steroid synthesis. The end products are mineralocorticoids, glucocorticoids, and sex steroids.

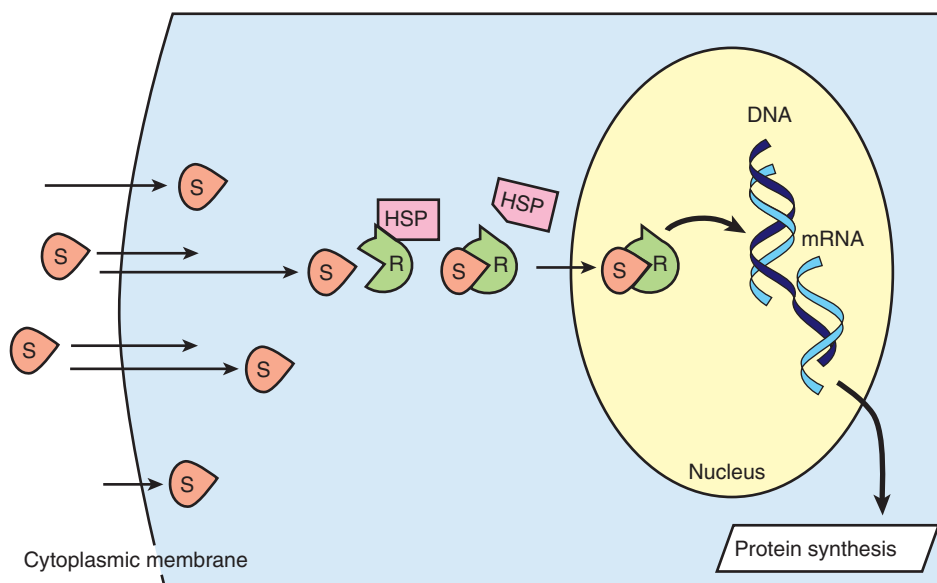


Figure 2-4. Simplified schematic of steroid transport into the nucleus. Steroid molecules (S) diffuse readily across cytoplasmic membranes. Intracellularly, the receptors (R) are rendered inactive by being coupled to heat shock protein (HSP). When S and R bind, HSP dissociates, and the S-R complex enters the nucleus, where the S-R complex induces DNA transcription, resulting in protein synthesis. mRNA = messenger RNA.

to the promoter regions of its target genes via a mechanism that involves histone deacetylase 2. In this way, glucocorticoids can inhibit a major mechanism by which TLR ligation induces proinflammatory gene expression.³⁵ The GR complex can also bind to specific nucleotide sequences (termed glucocorticoid response elements) to promote the transcription of genes that have anti-inflammatory functions. These include IL-10 and IL-1 receptor antagonist. Further, GR complex activation can indirectly influence TLR activity via an interaction with signaling pathways such as the mitogen-activated protein kinase and transforming growth factor-activated kinase-1 (TAK1) pathways. Finally, a recent report demonstrated that the GR complex can target both suppressor of cytokine signaling 1 (SOCS1) and type 1 IFNs to regulate TLR-induced STAT1 activation.³⁶

Adrenal insufficiency represents a clinical syndrome highlighted largely by inadequate amounts of circulating cortisol and aldosterone. Classically, adrenal insufficiency is described in patients with atrophic adrenal glands caused by exogenous steroid administration who undergo a stressor such as surgery. These patients subsequently manifest signs and symptoms such as tachycardia, hypotension, weakness, nausea, vomiting, and fever. Critical illness may be associated with a **relative adrenal insufficiency** such that the adrenal gland cannot mount an effective cortisol response to match the degree of injury. More recently, investigators have determined that critical illness-associated cortisol insufficiency in trauma patients occurs more frequently than previously thought.³⁷ It has a bimodal presentation in which the patient is at increased risk both early following the injury-associated inflammatory response and in a delayed fashion, with sepsis being the initiating event. Laboratory findings in adrenal insufficiency include hypoglycemia from decreased gluconeogenesis, hyponatremia from impaired renal tubular sodium resorption, and hyperkalemia from diminished kaliuresis. Rigorous testing to establish the diagnosis includes monitoring of basal and ACTH-stimulated cortisol levels, both of which are lower than normal during adrenal insufficiency. Treatment strategies remain controversial; however, they include low-dose steroid supplementation.³⁸

Macrophage Inhibitory Factor Modulates Cortisol Function. Macrophage inhibitory factor (MIF) is a proinflammatory

cytokine expressed by a variety of cells and tissues, including the anterior pituitary, macrophages, and T lymphocytes. Several important functions of MIF in innate and adaptive immune responses and in inflammation have been described, supporting the idea that MIF may function to counteract the anti-inflammatory activity of glucocorticoids.³⁹ For example, MIF has been reported to play a central role in the exacerbation of inflammation associated with acute lung injury, where it has been detected in the affected lungs and in alveolar macrophages. MIF has also been reported to upregulate the expression of TLR4 in macrophages.⁴⁰ Finally, an early increase in plasma MIF has been detected in severely injured patients and was found to correlate with NF- κ B translocation and respiratory burst in polymorphonuclear lymphocytes (PMNs) derived from severely injured patients. Further, nonsurvivors were shown to have higher serum MIF concentrations early after injury than survivors.⁴¹ These data suggest that targeting MIF after injury may be beneficial in preventing early PMN activation and subsequent organ failure in severely injured patients.

Growth Hormone, Insulin-Like Growth Factor, and Ghrelin.

Growth hormone (GH) is a neurohormone expressed primarily by the pituitary gland that has both metabolic and immunomodulatory effects. GH promotes protein synthesis and insulin resistance and enhances the mobilization of fat stores. GH secretion is upregulated by hypothalamic GH-releasing hormone and downregulated by somatostatin. GH primarily exerts its downstream effects through direct interaction with GH receptors and through the enhanced hepatic synthesis of insulin-like growth factor (IGF)-1, an anabolic growth factor that is known to improve the metabolic rate, gut mucosal function, and protein loss after traumatic injury. Less than 5% of IGF-1 circulates free in the plasma, with the remainder bound principally to one of six IGF-binding proteins (IGFBPs), the majority to IGFBP-3. In the liver, IGF stimulates protein synthesis and glycogenesis; in adipose tissue, it increases glucose uptake and lipid utilization; and in skeletal muscles, it mediates glucose uptake and protein synthesis. In addition to its effects on cellular metabolism, GH enhances phagocytic activity of immunocytes through increased lysosomal superoxide production. It also increases the

proliferation of T-cell populations.⁴² The catabolic state that follows severe injury has been linked to the suppression of the GH-IGF-IGFBP axis, as critical illness is associated with decreased circulating IGF levels. Not surprising, the administration of exogenous recombinant human GH (rhGH) has been studied in a prospective, randomized trial of critically ill patients where it was associated with increased mortality, prolonged ventilator dependence, and increased susceptibility to infection.⁴³ More recently, circulating GH levels were examined on admission in 103 consecutive critically ill adult patients. In this study, circulating GH levels were about seven-fold increased in the 24 nonsurvivors when compared with survivors, and GH level was an independent predictor of mortality, along with the APACHE II/SAPS II scores. In distinct contrast, the effect of rhGH administration in severely burned children, both acutely and following prolonged treatment, has been proven to be beneficial. Pediatric burn patients receiving rhGH demonstrated markedly improved growth and lean body mass, whereas hypermetabolism was significantly attenuated.⁴⁴ This finding was associated with significant increases in serum GH, IGF-1, and IGFBP-3.

Ghrelin, a natural ligand for the GH-secretagogue receptor 1a (GHS-R1a), is an appetite stimulant that is secreted by the stomach. GHS-R1a is expressed in a variety of tissues in different concentrations including the immune cells, B and T cells, and neutrophils. Ghrelin seems to play a role in promoting GH secretion and in glucose homeostasis, lipid metabolism, and immune function. In a rodent gut ischemia/reperfusion model, ghrelin administration inhibited proinflammatory cytokine release, reduced neutrophil infiltration, ameliorated intestinal barrier dysfunction, attenuated organ injury, and improved survival. It is interesting that this effect was dependent on an intact vagus nerve and that intracerebroventricular injection of ghrelin was also protective.⁴⁵ These data suggest that the effect of ghrelin is mediated via the CNS, most likely through the “cholinergic anti-inflammatory pathway.” More recently, high ghrelin levels were demonstrated in critically ill patients as compared to healthy controls, independent of the presence of inflammatory markers. Moreover, the high ghrelin levels were a positive predictor of intensive care unit survival in septic patients, matching previous results from animal models.

The Role of Catecholamines in Postinjury Inflammation.

Injury-induced activation of the sympathetic nervous system results in secretion of ACh from the preganglionic sympathetic fibers innervating the adrenal medulla. The adrenal medulla is a special case of autonomic innervation and is considered a **modified postganglionic neuron**. Thus, ACh signaling to the resident chromaffin cells ensures that a surge of epinephrine (EPI) and norepinephrine (NE) release into the circulation takes place in a ratio that is tightly regulated by both central and peripheral mechanisms. Circulating levels of EPI and NE are three- to four-fold elevated, an effect that persists for an extended time. The release of EPI can be modulated by transcriptional regulation of phenylethanolamine *N*-methyltransferase (PNMT), which catalyzes the last step of the catecholamine biosynthesis pathway methylating NE to form EPI. PNMT transcription, a key step in the regulation of EPI production, is activated in response to stress and tissue hypoxia by hypoxia-inducible factor 1 α (HIF1A).

Catecholamine release almost immediately prepares the body for the “fight or flight” response with well-described effects on the cardiovascular and pulmonary systems and on metabolism. These include increased heart rate, myocardial contractility, conduction velocity, and blood pressure; the redirection

of blood flow to skeletal muscle; increased cellular metabolism throughout the body; and mobilization of glucose from the liver via glycogenolysis, gluconeogenesis, lipolysis, and ketogenesis. To compound the resulting hyperglycemia, insulin release is decreased mainly through the stimulation of α -adrenergic pancreatic receptors. Hyperglycemia, as will be discussed later, contributes to the proinflammatory response and to further mitochondrial dysfunction.

The goal of this well-orchestrated catecholamine response is to re-establish and maintain the systems’ homeostasis, including the innate immune system. Circulating catecholamines can directly influence inflammatory cytokine production.⁴⁶ Data indicate that basal EPI levels condition the activity and responsiveness of cytokine-secreting cells, which may explain large interindividual variability in innate cytokine profiles observed following injury. Epinephrine infusion at higher doses has been found to inhibit production of TNF- α in vivo and to enhance the production of the anti-inflammatory cytokine IL-10.⁴⁷ Additionally, *in vitro* studies indicate that stress levels of glucocorticoids and EPI, acting in concert, can inhibit production of IL-12, a potent stimulator of Th1 responses. Further, they have been shown in vitro to decrease Th1 cytokine production and increase Th2 cytokine production to a significantly greater degree compared to either adrenal hormone alone. Thus, catecholamines secreted from the adrenal gland, specifically EPI, play a role in both innate proinflammatory cytokine regulation and adaptive Th responses, and may act in concert with cortisol during the injury response to modulate cytokine activity.⁴⁸

How are these effects explained? It is well established that a variety of human immune cells (e.g., mononuclear cells, macrophages, granulocytes) express adrenergic receptors that are members of the family of G-protein-coupled receptors that act through the activation of intracellular second messengers such as cyclic adenosine monophosphate (cAMP) and calcium ion influx (discussed in more detail later). These second messengers can regulate a variety of immune cell functions, including the release of inflammatory cytokines and chemokines.

The sympathetic nervous system also has direct immunomodulatory properties via its innervation of lymphoid tissues that contain resting and activated immune cells. With stimulation of these postganglionic nerves, NE is released where it can interact with β_2 -adrenergic receptors expressed by CD4⁺ T and B lymphocytes, many of which also express α_2 -adrenergic receptors. Additionally, endogenous catecholamine expression has been detected in these cells, as has the machinery for catecholamine synthesis. For example, human peripheral blood mononuclear cells contain inducible mRNA for the catecholamine-generating enzymes, tyrosine-hydroxylase and dopamine- β -hydroxylase, and data suggest that cells can regulate their own catecholamine synthesis in response to extracellular cues. Exposure of peripheral blood mononuclear cells to NE triggers a distinct genetic profile that indicates a modulation of Th cell function. What the net effect of dopamine, NE, and EPI synthesis by circulating and resident immune cells may be relative to that secreted by the adrenal medulla is not clear and is an area that would certainly benefit from ongoing research efforts to identify novel therapeutic targets.

Aldosterone. Aldosterone is a mineralocorticoid released by the zona glomerulosa of the adrenal cortex. It binds to the mineralocorticoid receptor (MR) of principal cells in the collecting duct of the kidney where it can stimulate expression of genes involved in sodium reabsorption and potassium excretion

to regulate extracellular volume and blood pressure. MRs have also been shown to have effects on cell metabolism and immunity. For example, recent studies show aldosterone interferes with insulin signaling pathways and reduces expression of the insulin-sensitizing factors, adiponectin and peroxisome proliferator activated receptor- γ (PPAR- γ), which contribute to insulin resistance. In the immune system, mononuclear cells, such as monocytes and lymphocytes, have been shown to possess an MR that binds aldosterone with high specificity, regulating sodium and potassium flux, as well as plasminogen activator inhibitor-1 and p22 phox expression, in these cells.⁴⁹ Further, aldosterone inhibits cytokine-mediated NF- κ B activation in neutrophils, which also possess a functional MR.


Insulin. Hyperglycemia and insulin resistance are hallmarks of injury and critical illness due to the catabolic effects of circulating mediators, including catecholamines, cortisol, glucagon, and GH. The increase in these circulating proglycemic factors, particularly EPI, induces glycogenolysis, lipolysis, and increased lactate production independent of available oxygen in a process that is termed “aerobic glycolysis.” Although there is an increase in insulin production at the same time, severe stress is frequently associated with **insulin resistance**, leading to decreased glucose uptake in the liver and the periphery contributing to acute hyperglycemia. Insulin is a hormone secreted by the pancreas, which mediates an overall host anabolic state through hepatic glycogenesis and glycolysis, peripheral glucose uptake, lipogenesis, and protein synthesis.⁵⁰

The insulin receptor (IR) is widely expressed and consists of two isoforms, which can form homo- or heterodimers with insulin binding. Dimerization leads to receptor autophosphorylation and activation of intrinsic tyrosine kinase activity. Downstream signaling events are dependent on the recruitment of the adaptor proteins, insulin receptor substrate (IRS-1), and Shc to the IR. Systemic insulin resistance likely results from proinflammatory signals, which modulate the phosphorylation of IRS-1 to affect its function.

Hyperglycemia during critical illness is predictive of increased mortality in critically ill trauma patients.⁵¹ It can modulate the inflammatory response by altering leukocyte functions, and the resulting decreases in phagocytosis, chemotaxis, adhesion, and respiratory burst activities are associated with an increased risk for infection. In addition, glucose administration results in a rapid increase in NF- κ B activation and proinflammatory cytokine production. Insulin therapy to manage hyperglycemia has grown in favor and has been shown to be associated with both decreased mortality and a reduction in infectious complications in select patient populations. However, the trend toward tight glycemic control in the intensive care unit failed to show benefit when examined in several reviews.⁵² Thus, the ideal blood glucose range within which to maintain critically ill patients and to avoid hypoglycemia has yet to be determined.

THE CELLULAR STRESS RESPONSES

Reactive Oxygen Species and the Oxidative Stress Response

Reactive oxygen and nitrogen species (ROS and RNS, respectively) are small molecules that are highly reactive due to the presence of unpaired outer orbit electrons. They can cause cellular injury to both host cells and invading pathogens through  the oxidation of cell membrane substrates. Oxygen radicals

are produced as a by-product of oxygen metabolism in the mitochondria as well as by processes mediated by cyclooxygenases, NADPH oxidase (NOX), and xanthine oxidase. The main areas of ROS production include mitochondrial respiratory chain, peroxisomal fatty acid metabolism, cytochrome P450 reactions, and the respiratory burst of phagocytic cells. In addition, protein folding in the endoplasmic reticulum can also result in the formation of ROS.⁵³ Potent oxygen radicals include oxygen, superoxide, hydrogen peroxide, and hydroxyl radicals. RNS include NO and nitrite. The synthesis of ROS is regulated at several checkpoints and via several signaling mechanisms, including Ca²⁺ signaling, phosphorylation, and small G protein activation, which influence both the recruitment of the molecules required for NOX function and the synthesis of ROS in the mitochondria. NOX activation is triggered by a number of inflammatory mediators (e.g., TNF, chemokines, lysophospholipids, complement, and leukotrienes). Host cells are protected from the damaging effects of ROS through a number of mechanisms. The best described of these is via the upregulation and/or activation of endogenous antioxidant proteins. However, pyruvate kinase also provides negative feedback for ROS synthesis, as do molecules that react nonenzymatically with ROS. Under normal physiologic conditions, ROS production is balanced by these antioxidative strategies. In this context, ROS can act effectively as signaling molecules through their ability to modulate cysteine residues by oxidation and thus influence the functionality of target proteins.⁵⁴ This has recently been described as a mechanism in the regulation of phosphatases. ROS can also contribute to transcription activity both indirectly, through its effects on transcription factor lifespan, and directly, through the oxidation of DNA. An important role for ROS has been well described in phagocytes, which use these small molecules for pathogen killing. Recent data, however, indicate that ROS may mediate inflammasome activation by diverse agonists.⁵⁵ In addition, ROS appear to be involved in adaptive immunity. They have been described as a prime source of phosphatase activation in both B and T lymphocytes, which can regulate the function of key receptors and intracellular signaling molecules in these cells by affecting phosphorylation events.

The Heat Shock Response

Heat shock proteins (HSPs) are a group of intracellular proteins that are increasingly expressed during times of stress, such as burn injury, inflammation, oxidative stress, and infection. HSPs are expressed in the cytoplasm, nucleus, endoplasmic reticulum, and mitochondria, where they function as molecular chaperones that help monitor and maintain appropriate protein folding.⁵⁶ HSPs accomplish this task through the promotion of protein refolding, the targeting of misfolded proteins for degradation, and the assistance of partially folded proteins to appropriate membrane compartments. HSPs bind also bind foreign proteins and thereby function as intracellular chaperones for ligands such as bacterial DNA and endotoxin. HSPs are presumed to protect cells from the effects of traumatic stress and, when released by damaged cells, alert the immune system of the tissue damage. However, depending on their location and the type of immune cell in which they are expressed, HSPs may exert proinflammatory immune activating signals or anti-inflammatory immune dampening signals (Table 2-4).⁵⁷

The Unfolded Protein Response

Secreted, membrane-bound, and organelle-specific proteins fold in the lumen of the endoplasmic reticulum (ER) where they also

TABLE 2-4

The immunomodulatory functions of heat shock proteins (HSPs)

	CELL LOCATION	RECOGNIZED AS DAMP?	IMMUNOMODULATORY FUNCTION
HSP90	Cytoplasm, endoplasmic reticulum Can function both inside and outside the cell	May act as DAMP chaperone to activate innate immune response	Binds and optimizes RNA polymerase II action to regulate gene transcription Stabilizes glucocorticoid receptor in the cytoplasm Important for processing and membrane expression of TLR Chaperones include IKK Facilitates antigen presentation to dendritic cells
HSP70	Can function both inside and outside the cell Endoplasmic reticulum homolog is BiP	Exogenous HSP70 elicits cellular calcium flux, NF- κ B activation, cytokine production	Can have anti-inflammatory actions when expression is increased Inhibits TLR-mediated cytokine production via NF- κ B Reduces dendritic cell capacity for T-cell stimulation BiP sequesters proteins important to the unfolded protein response
HSP60	Mitochondria	Exogenous HSP60 inhibits NF- κ B activation	Plays a role in intracellular protein trafficking Modulates cytokine synthesis

BiP = binding immunoglobulin protein; DAMP = damage-associated molecular pattern; IKK = I κ B kinase; NF- κ B, nuclear factor- κ B; TLR = toll-like receptor

receive their posttranslational modifications. Millimolar calcium concentrations are required to maintain the normal cellular protein folding capacity. Cellular stress decreases calcium concentration in the ER, disrupting the machinery required for this process and leading to the accumulation of misfolded or unfolded proteins. These occurrences are sensed by a highly conserved array of signaling proteins in the ER, including inositol requiring enzyme 1 (IRE1), protein kinase RNA (PKR)-like ER kinase (PERK), and activating transcription factor 6 (ATF6). Together, this complex generates the **unfolded protein response** (UPR), a mechanism by which ER distress signals are sent to the nucleus to modulate transcription in an attempt to restore homeostasis. Prolongation of the UPR, indicative of irreversible cellular damage, can result in cell death. Genes activated in the UPR result not only in the inhibition of translation, but also other potentially immunomodulatory events including induction of the acute-phase response, activation of NF- κ B, and the generation of antibody-producing B cells.⁵⁸

Burn injury leads to the marked reduction in ER calcium levels and activation of UPR sensing proteins. Moreover, recent data in a series of burn patients strongly link the UPR to insulin resistance and hyperglycemia in these patients.⁵⁹ Thus, a better understanding of the UPR, which is triggered by severe inflammation, may allow the identification of novel therapeutic targets for injury-associated insulin resistance.

Autophagy

Under normal circumstances, cells need to have a way of disposing of damaged organelles and debris aggregates that are too large to be managed by proteasomal degradation. In order to accomplish this housekeeping task, cells use a process referred to as “macroautophagy” (**autophagy**), which is thought to have originated as a stress response.⁶⁰ The steps of autophagy include the engulfment of cytoplasm/organelle by an “isolation membrane,” which is also called a phagophore. The edges of the phagophore then fuse to form the autophagosome, a double-membraned vesicle that sequesters the cytoplasmic material and that is a characteristic feature of autophagy. The autophagosome then fuses with a lysosome to form an autolysosome where the

contents, together with the inner membrane, are degraded. This process is controlled by numerous autophagy-specific genes and by the specific kinase, mammalian target of rapamycin (mTOR).

As noted earlier, autophagy is a normal cellular process that occurs in quiescent cells for cellular maintenance. However, under conditions of hypoxia and low cellular energy, autophagy is induced in an attempt to provide additional nutrients for energy production. The induction of autophagy promotes a shift from aerobic respiration to glycolysis and allows cellular components of the autophagosome to be hydrolyzed to energy substrates. Increased levels of autophagy are typical in activated immune cells and are a mechanism for the disposal of ROS and phagocytosed debris.

Recent data support the idea that autophagy may also play an important role in the immune response.⁶¹ Autophagy is stimulated by Th1 cytokines and with activation of TLR in macrophages, but is inhibited by Th2 cytokines. It is also recognized as an important regulator of cytokine secretion, particularly those cytokines of the IL-1 family that are dependent on inflammasome processing for activation. For example, autophagosomes can sequester and degrade pro-IL-1 β and inflammasome components. In animal models of sepsis, inhibition of autophagy results in increased proinflammatory cytokine levels that correlate with increased mortality.⁶² These data suggest that autophagy is a protective mechanism whereby the cell can regulate the levels of cytokine production.

Apoptosis

Apoptosis (regulated cell death) is an energy-dependent, organized mechanism for clearing senescent or dysfunctional cells, including macrophages, neutrophils, and lymphocytes, without promoting an inflammatory response. This contrasts with cellular necrosis that results in disorganized intracellular molecule release with subsequent immune activation and inflammatory response. Systemic inflammation modulates apoptotic signaling in active immunocytes, which subsequently influences the inflammatory response through the loss of effector cells.

Apoptosis proceeds primarily through two pathways: the extrinsic pathway and the intrinsic pathway. The extrinsic

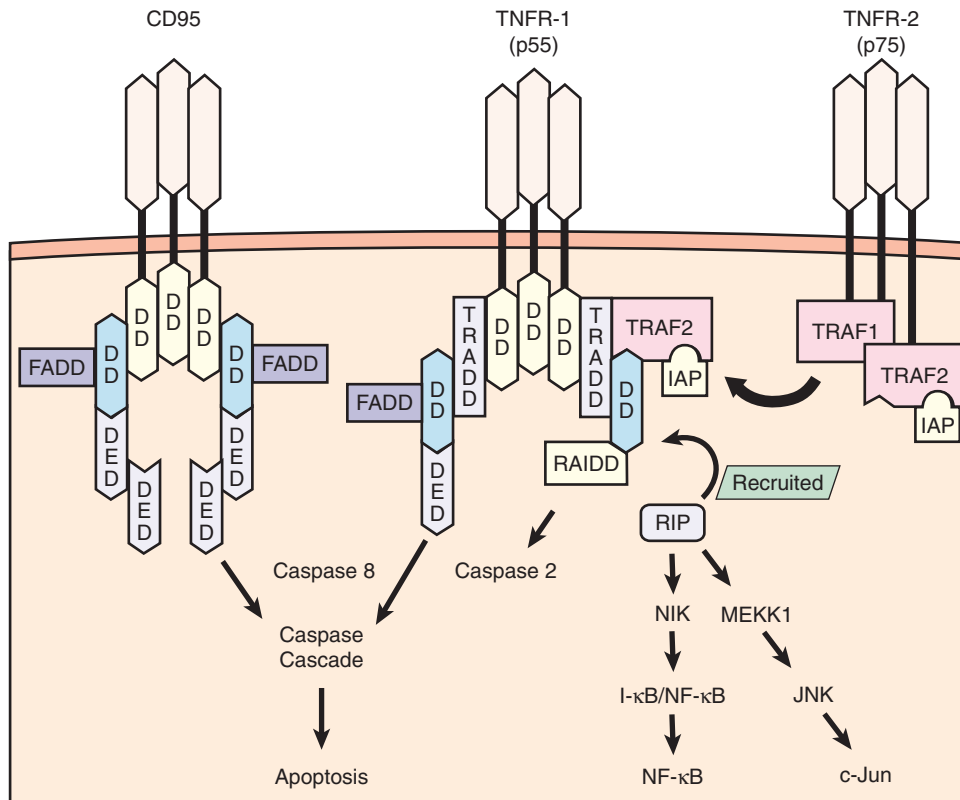


Figure 2-5. Signaling pathway for tumor necrosis factor receptor 1 (TNFR-1) (55 kDa) and TNFR-2 (75 kDa) occurs by the recruitment of several adapter proteins to the intracellular receptor complex. Optimal signaling activity requires receptor trimerization. TNFR-1 initially recruits TNFR-associated death domain (TRADD) and induces apoptosis through the actions of proteolytic enzymes known as *caspases*, a pathway shared by another receptor known as *CD95 (Fas)*. CD95 and TNFR-1 possess similar intracellular sequences known as *death domains (DDs)*, and both recruit the same adapter proteins known as *Fas-associated death domains (FADDs)* before activating caspase 8. TNFR-1 also induces apoptosis by activating caspase 2 through the recruitment of receptor-interacting protein (RIP). RIP also has a functional component that can initiate nuclear factor-κB (NF-κB) and c-Jun activation, both favoring cell survival and proinflammatory functions. TNFR-2 lacks a DD component but recruits adapter proteins known as TNFR-associated factors 1 and 2 (TRAF1, TRAF2) that interact with RIP to mediate NF-κB and c-Jun activation. TRAF2 also recruits additional proteins that are antiapoptotic, known as inhibitors of apoptosis proteins (IAPs). DED = death effector domain; I-κB = inhibitor of κB; I-κB/NF-κB = inactive complex of NF-κB that becomes activated when the I-κB portion is cleaved; JNK = c-Jun N-terminal kinase; MEKK1 = mitogen-activated protein/extracellular regulatory protein kinase kinase kinase-1; NIK = NF-κB-inducing kinase; RAIDD = RIP-associated interleukin-1b-converting enzyme and ced-homologue-1-like protein with death domain, which activates proapoptotic caspases. (Adapted with permission from Lin E, Calvano SE, Lowry SF. Tumor necrosis factor receptors in systemic inflammation. In: Vincent J-L (series ed), Marshall JC, Cohen J, eds. Update in Intensive Care and Emergency Medicine: Vol. 31: Immune Response in Critical Illness. Berlin: Springer-Verlag; 2002:365. With kind permission from Springer Science + Business Media.)

pathway is activated through the binding of death receptors (e.g., Fas, TNFR), which leads to the recruitment of Fas-associated death domain protein and subsequent activation of caspase 3 (Fig. 2-5). On activation, caspases are the effectors of apoptotic signaling because they mediate the organized breakdown of nuclear DNA. The intrinsic pathway proceeds through protein mediators (e.g., Bcl-2, Bcl-2-associated death promoter, Bcl-2-associated X protein, Bim) that influence mitochondrial membrane permeability. Increased membrane permeability leads to the release of mitochondrial cytochrome C, which ultimately activates caspase 3 and thus induces apoptosis. These pathways do not function in a completely autonomous manner, because there is significant interaction and crosstalk between mediators of both extrinsic and intrinsic pathways. Apoptosis is modulated by several regulatory factors, including inhibitors of apoptosis proteins and regulatory caspases (e.g., caspases 1, 8, 10).

Apoptosis during sepsis may influence the ultimate competency of the acquired immune response. In a murine model of peritoneal sepsis, increased lymphocyte apoptosis was

associated with mortality, which may be due to a resultant decrease in IFN-γ release. In postmortem analysis of patients who expired from overwhelming sepsis, there was an increase in lymphocyte apoptosis, whereas macrophage apoptosis did not appear to be affected. Clinical trials have observed an association between the degree of lymphopenia and disease severity in sepsis. In addition, after the phagocytosis of apoptotic cells by macrophages, anti-inflammatory mediators such as IL-10 are released that may exacerbate immune suppression during sepsis. Neutrophil apoptosis is inhibited by inflammatory products, including TNF, IL-1, IL-3, IL-6, granulocyte-macrophage colony-stimulating factor (GM-CSF), and IFN-γ. This retardation in regulated cell death may prolong and exacerbate secondary injury through neutrophil free radical release as the clearance of senescent cells is delayed.⁶³

Necroptosis

Cellular necrosis refers to the premature uncontrolled death of cells in living tissue typically caused by accidental exposure

to external factors, such as ischemia, inflammation, or trauma, which result in extreme cellular stress. Necrosis is characterized by the loss of plasma membrane integrity and cellular collapse with extrusion of cytoplasmic contents, but the cell nuclei typically remain intact. Recent data have defined a process by which necrosis occurs through a series of well-described steps that are dependent on a signaling pathway that involves the receptor-interacting protein kinase (RIPK) complex. Termed “necroptosis,” it occurs in response to specific stimuli, such as TNF- and TLR-mediated signals.⁶⁴ For example, ligation of the TNF receptor 1 (TNFR1) under conditions in which caspase 8 is inactivated (e.g., by pharmacologic agents) results in the overgeneration of ROS and a metabolic collapse. The net result is programmed necrosis (necroptosis). The effect of cell death by necroptosis on the immune response is not yet known. However, it is likely that the “DAMP” signature that occurs in response to necroptotic cell death is an important contributor to the systemic inflammatory response. Evidence to support this concept was provided by investigators who examined the role of necroptosis in murine models of sepsis. They demonstrated that *Ripk3*^{-/-} mice were capable of recovering body temperature better, exhibited lower circulating DAMP levels, and survived at higher rates than their wild-type littermates.⁶⁵ These data suggest that the cellular damage that occurs with programmed necrosis exacerbates the sepsis-associated systemic inflammatory response.

MEDIATORS OF INFLAMMATION

Cytokines

Cytokines are a class of protein signaling compounds that are essential for both innate and adaptive immune responses. Cytokines mediate a broad sequence of cellular responses, including cell migration, DNA replication, cell turnover, and immunocyte proliferation (Table 2-5). When functioning locally at the site of injury and infection, cytokines mediate the eradication of invading microorganisms and also promote wound healing. However, an exaggerated proinflammatory cytokine response to inflammatory stimuli may result in hemodynamic instability (i.e., septic shock) and metabolic derangements (i.e., muscle wasting). Anti-inflammatory cytokines also are released, at least in part, as an opposing influence to the proinflammatory cascade. These anti-inflammatory mediators may also result in immunocyte dysfunction and host immunosuppression. Cytokine signaling after an inflammatory stimulus can best be represented as a finely tuned balance of opposing influences and should not be oversimplified as a “black and white” proinflammatory/anti-inflammatory response. A brief discussion of the important cytokine molecules is included.

Tumor Necrosis Factor- α . TNF- α is a cytokine that is rapidly mobilized in response to stressors such as injury and infection and is a potent mediator of the subsequent inflammatory response. TNF is primarily synthesized by immune cells, such as macrophages, dendritic cells, and T lymphocytes, but nonimmune cells have also been reported to secrete low amounts of the cytokine.

TNF is generated in a precursor form called transmembrane TNF that is expressed as a trimer on the surface of activated cells. After being processed by the metalloproteinase TNF- α -converting enzyme (TACE; also known as ADAM-17), a smaller, soluble form of TNF is released, which mediates its biologic activities through type 1 and 2 TNF receptors

(TNFR1; TNFR2).⁶⁶ Transmembrane TNF- α also binds to TNFR1 and TNFR2, but its biologic activities are likely mediated through TNFR2. While the two receptors share homology in their ligand binding regions, there are distinct differences that regulate their biologic function. For example, TNFR1 is expressed by a wide variety of cells but is typically sequestered in the Golgi complex. Following appropriate cell signaling, TNFR1 is mobilized to the cell surface, where it sensitizes cells to TNF, or it can be cleaved from the surface in the form of a soluble receptor that can neutralize TNF.⁶⁷ In contrast, TNFR2 expression is confined principally to immune cells where it resides in the plasma membrane. Both TNF receptors are capable of binding intracellular adaptor proteins that lead to activation of complex signaling processes and mediate the effects of TNF.

Although the circulating half-life of soluble TNF is brief, it acts upon almost every differentiated cell type, eliciting a wide range of important cellular responses. In particular, TNF elicits many metabolic and immunomodulatory activities. It stimulates muscle breakdown and cachexia through increased catabolism, insulin resistance, and redistribution of amino acids to hepatic circulation as fuel substrates. TNF also mediates coagulation activation, cell migration, and macrophage phagocytosis, and enhances the expression of adhesion molecules, prostaglandin E₂, platelet-activating factor, glucocorticoids, and eicosanoids. Recent studies indicate that a significant early TNF response after trauma may be associated with improved survival in these patients.⁶⁸

Interleukin-1. IL-1 α and IL-1 β , which are encoded by two distinct IL-1 genes, were the first described members of the IL-1 cytokine family. Currently, the family has expanded to 11 members, with the three major forms being IL-1 α , IL-1 β , and IL-1 receptor antagonist (IL-1R α). IL-1 α and IL-1 β share similar biologic functions, but have limited sequence homology. They use the same cell surface receptor, termed IL-1 receptor type 1 (IL-1R1), which is present on nearly all cells. Although IL-1R α is synthesized and released in response to the same stimuli that lead to IL-1 production, it lacks the necessary domain to form a bioactive complex with the IL-1 receptor when bound. Thus, IL-1R α serves as a competitive antagonist for the receptor. IL-1R activation initiates signaling events, which result in the synthesis and release of a variety of inflammatory mediators.

The IL-1 α precursor is constitutively expressed and stored in a variety of healthy cells, including epithelium, endothelium, and platelets. Both the precursor and mature forms of IL-1 α are active. With appropriate signals, IL-1 α moves to the cell membrane where it can act on adjacent cells bearing the IL-1 receptor. It can also be released directly from injured cells. In this way, IL-1 α is believed to function as a DAMP, which promotes the synthesis of inflammatory mediators, such as chemokines and eicosanoids. These mediators attract neutrophils to the injured site, facilitate their exit from the vasculature, and promote their activation. Once they have reached their target, neutrophil lifespan is extended by the presence of IL-1 α .⁶⁹

IL-1 β , a multifunctional proinflammatory cytokine, is not detectable in healthy cells. Rather, its expression and synthesis occur in a more limited number of cells, such as monocytes, tissue macrophages, and dendritic cells, following their activation. IL-1 β expression is tightly regulated at multiple levels (e.g., transcription, translation, and secretion), although the rate-limiting step is its transcription. IL-1 β is synthesized and released in response to inflammatory stimuli, including cytokines

Table 2-5

Cytokines and their sources

CYTOKINE	SOURCE	COMMENT
TNF	<i>Macrophages/monocytes</i> Kupffer cells Neutrophils NK cells Astrocytes Endothelial cells T lymphocytes Adrenal cortical cells Adipocytes Keratinocytes Osteoblasts Mast cells Dendritic cells	Among earliest responders after injury; half-life <20 min; activates TNF receptors 1 and 2; induces significant shock and catabolism
IL-1	<i>Macrophages/monocytes</i> B and T lymphocytes NK cells Endothelial cells Epithelial cells Keratinocytes Fibroblasts Osteoblasts Dendritic cells Astrocytes Adrenal cortical cells Megakaryocytes Platelets Neutrophils Neuronal cells	Two forms (IL-1 α and IL-1 β); similar physiologic effects as TNF; induces fevers through prostaglandin activity in anterior hypothalamus; promotes β -endorphin release from pituitary; half-life <6 min
IL-2	<i>T lymphocytes</i>	Promotes lymphocyte proliferation, immunoglobulin production, gut barrier integrity; half-life <10 min; attenuated production after major blood loss leads to immunocompromise; regulates lymphocyte apoptosis
IL-3	<i>T lymphocytes</i> Macrophages Eosinophils Mast cells	
IL-4	<i>T lymphocytes</i> Mast cells Basophils Macrophages B lymphocytes Eosinophils Stromal cells	Induces B-lymphocyte production of IgG4 and IgE, mediators of allergic and anthelmintic response; downregulates TNF, IL-1, IL-6, IL-8
IL-5	<i>T lymphocytes</i> Eosinophils Mast cells Basophils	Promotes eosinophil proliferation and airway inflammation
IL-6	<i>Macrophages</i> B lymphocytes Neutrophils Basophils Mast cells Fibroblasts Endothelial cells Astrocytes	Elicited by virtually all immunogenic cells; long half-life; circulating levels proportional to injury severity; prolongs activated neutrophil survival

(Continued)

Table 2-5

Cytokines and their sources (continued)

CYTOKINE	SOURCE	COMMENT
	Synovial cells Adipocytes Osteoblasts Megakaryocytes Chromaffin cells Keratinocytes	
IL-8	<i>Macrophages/monocytes</i> T lymphocytes Basophils Mast cells Epithelial cells Platelets	Chemoattractant for neutrophils, basophils, eosinophils, lymphocytes
IL-10	<i>T lymphocytes</i> B lymphocytes Macrophages Basophils Mast cells Keratinocytes	Prominent anti-inflammatory cytokine; reduces mortality in animal sepsis and ARDS models
IL-12	<i>Macrophages/monocytes</i> Neutrophils Keratinocytes Dendritic cells B lymphocytes	Promotes Th1 differentiation; synergistic activity with IL-2
IL-13	<i>T lymphocytes</i>	Promotes B-lymphocyte function; structurally similar to IL-4; inhibits nitric oxide and endothelial activation
IL-15	<i>Macrophages/monocytes</i> Epithelial cells	Anti-inflammatory effect; promotes lymphocyte activation; promotes neutrophil phagocytosis in fungal infections
IL-18	<i>Macrophages</i> Kupffer cells Keratinocytes Adrenal cortical cells Osteoblasts	Similar to IL-12 in function; levels elevated in sepsis, particularly gram-positive infections; high levels found in cardiac deaths
IFN- γ	<i>T lymphocytes</i> NK cells Macrophages	Mediates IL-12 and IL-18 function; half-life of days; found in wounds 5–7 d after injury; promotes ARDS
GM-CSF	<i>T lymphocytes</i> Fibroblasts Endothelial cells Stromal cells	Promotes wound healing and inflammation through activation of leukocytes
IL-21	<i>T lymphocytes</i>	Preferentially secreted by Th2 cells; structurally similar to IL-2 and IL-15; activates NK cells, B and T lymphocytes; influences adaptive immunity
HMGB1	<i>Monocytes/lymphocytes</i>	High mobility group box chromosomal protein; DNA transcription factor; late (downstream) mediator of inflammation (ARDS, gut barrier disruption); induces “sickness behavior”

ARDS = acute respiratory distress syndrome; GM-CSF = granulocyte-macrophage colony-stimulating factor; IFN = interferon; Ig = immunoglobulin; IL = interleukin; NK = natural killer; Th1 = helper T cell subtype 1; Th2 = helper T cell subtype 2; TNF = tumor necrosis factor.

(TNF, IL-18) and foreign pathogens. IL-1 α or IL-1 β itself can also induce IL-1 β transcription. In contrast to IL-1 α , IL-1 β is synthesized as an inactive precursor molecule. The formation of mature IL-1 β requires the assembly of the inflammasome complex by the cell and the activation of caspase 1, which is required for the processing of stored pro-IL-1 β . Mature IL-1 β

is then released from the cell via an unconventional secretory pathway. IL-1 β has a spectrum of proinflammatory effects that are largely similar to those induced by TNF, and injection of IL-1 β alone is sufficient to induce inflammation. High doses of either IL-1 β or TNF are associated with profound hemodynamic compromise. Interestingly, low doses of both IL-1 β and TNF

combined elicit hemodynamic events similar to those elicited by high doses of either mediator, which suggests a synergistic effect.

There are two primary receptor types for IL-1: IL-1R1 and IL-1R2. IL-1R1 is widely expressed and mediates inflammatory signaling on ligand binding. IL-1R2 is proteolytically cleaved from the membrane surface to soluble form on activation and thus serves as another mechanism for competition and regulation of IL-1 activity. IL-1 α or IL-1 β binds first to IL-1R1. This is followed by recruitment of a transmembrane coreceptor, termed the IL-1R accessory protein (IL-1RAcP). A complex is formed of IL-1R1 plus IL-1 plus the coreceptor. The signal is initiated with recruitment of the adaptor protein MyD88 to the toll-IL-1 receptor (TIR) domains of the receptor complex and signal transduction then occurs via intermediates, which are homologous to the signal cascade initiated by TLRs. These events culminate in the activation of NF- κ B and its nuclear translocation.⁷⁰

Interleukin-2. IL-2 is a multifunctional cytokine produced primarily by CD4⁺ T cells after antigen activation, which plays a pivotal role in the immune response. Other cellular sources for IL-2 include CD8⁺ and NK T cells, mast cells, and activated dendritic cells. Discovered as a T-cell growth factor, IL-2 also promotes CD8⁺ T-cell and NK cell cytolytic activity and modulates T-cell differentiation programs in response to antigen. Thus, IL-2 promotes naïve CD4⁺ T-cell differentiation into T helper 1 (Th1) and T helper 2 (Th2) cells while inhibiting T helper 17 (Th17) and T follicular helper (Tfh) cell differentiation. Moreover, IL-2 is essential for the development and maintenance of T regulatory (Treg) cells and for activation-induced cell death, thereby mediating tolerance and limiting inappropriate immune reactions. The upregulation of IL-2 requires calcium as well as protein kinase C signaling, which leads to the activation of transcription factors such as nuclear factor of activated T cells (NFAT) and NF- κ B. MicroRNAs also play a role in the regulation of IL-2 expression.⁷¹

IL-2 binds to IL-2 receptors (IL-2R), which are expressed on leukocytes. IL-2Rs are formed from various combinations of three receptor subunits: IL-2R α , IL-2R β , and IL-2R γ ; these form low-, medium-, and high-affinity forms of the receptor depending on the subunit combination. IL-2R γ has been renamed the common cytokine receptor γ chain (γ_c), which is now known to be shared by IL-2, IL-4, IL-7, IL-9, IL-15, and IL-21. Constitutive IL-2 receptor expression is low and is inducible by T-cell receptor ligation and cytokine stimulation. Importantly, the transcription of each receptor subunit is individually regulated via a complex process to effect tight control of surface expression. Once the receptor is ligated, the major IL-2 signaling pathways that are engaged include Janus kinase (JAK) signal transducer and activator of transcription (STAT), Shc-Ras-MAPK, and phosphoinositol-3-kinase (PI3K)-AKT. Partly due to its short half-life of <10 minutes, IL-2 is not readily detectable after acute injury. IL-2 receptor blockade induces immunosuppressive effects and can be pharmacologically used for organ transplantation. Attenuated IL-2 expression observed during major injury or blood transfusion may contribute to the relatively immunosuppressed state of the surgical patient.⁷²

Interleukin-6. Following burn or traumatic injury, DAMPs from damaged or dying cells stimulate TLRs to produce IL-6, a pleiotropic cytokine that plays a central role in host defense. IL-6 levels in the circulation are detectable by 60 minutes, peak

between 4 and 6 hours, and can persist for as long as 10 days. Further, plasma levels of IL-6 are proportional to the degree of injury. In the liver, IL-6 strongly induces a broad spectrum of acute-phase proteins such as CRP and fibrinogen, among others, whereas it reduces expression of albumin, cytochrome P450, and transferrin. In lymphocytes, IL-6 induces B-cell maturation into immunoglobulin-producing cells and regulates Th17/Treg balance. IL-6 modulates T-cell behavior by inducing the development of Th17 cells and inhibiting Treg cell differentiation in conjunction with transforming growth factor- β . IL-6 also promotes angiogenesis and increased vascular permeability, which are associated with local inflammatory responses. To date, 10 IL-6 family cytokines have been identified, including IL-6, oncostatin M, neuropoietin, IL-11, IL-27, and IL-31, all of which use trans signaling.⁷³

The IL-6 receptor (IL-6R, gp80) is expressed on hepatocytes, monocytes, B cells, and neutrophils in humans. However, many other cells respond to IL-6 through a process known as trans signaling.⁷⁴ In this case, soluble IL-6Rs (sIL-6R) exist in the serum and bind to IL-6, forming an IL-6/sIL-6R complex. The soluble receptor is produced by proteolytic cleavage from the surface of neutrophils in a process that is stimulated by CRP, complement factors, and leukotrienes. The IL-6/sIL-6R complex can then bind to the gp130 receptor, which is expressed ubiquitously on cells. Upon IL-6 stimulation, gp130 transduces two major signaling pathways: the JAK-STAT3 pathway and the SHP2-Gab-Ras-Erk-MAPK pathway, which is regulated by cytoplasmic suppressor of cytokine signaling (SOCS3). These signaling events can lead to increased expression of adhesion molecules as well as proinflammatory chemokines and cytokines. High plasma IL-6 levels have been associated with mortality during intra-abdominal sepsis.⁷⁵

Interleukin-10. We have talked almost exclusively about the factors that initiate the inflammatory response following cellular stress or injury. The re-establishment of immune homeostasis following these events requires the resolution of inflammation and the initiation of tissue repair processes. IL-10 plays a central role in this anti-inflammatory response by regulating the duration and magnitude of inflammation in the host.

The IL-10 family currently has six members including IL-10, IL-19, IL-20, IL-22, IL-24, and IL-26. IL-10 is produced by a variety of immune cells of both myeloid and lymphoid origin. Its synthesis is upregulated during times of stress and systemic inflammation; however, each cell type that produces IL-10 does so in response to different stimuli, allowing for tight control of its expression. IL-10 exerts effects by binding to the IL-10 receptor (IL-10R), which is a tetramer formed from two distinct subunits, IL-10R1 and IL-10R2. Specifically, IL-10 binds first to the IL-10R1 subunit, which then recruits IL-10R2, allowing the receptor complex to form. Whereas IL-10R2 is widely expressed, IL-10R1 expression is confined to leukocytes so that this differential expression of the receptor confines the effects of IL-10 to the immune system. Once receptor ligation occurs, signaling proceeds by the activation of JAK1 and STAT3. In particular, STAT3 in conjunction with IL-10 is absolutely required for the transcription of genes responsible for the anti-inflammatory response. IL-10 inhibits the secretion of proinflammatory cytokines, including TNF and IL-1, partly through the downregulation of NF- κ B, and thereby functions as a negative feedback regulator of the inflammatory cascade.⁷⁶ In macrophages, IL-10 suppresses the transcription of 20% of all lipopolysaccharide (LPS)-induced genes. Further, experimental

models of inflammation have shown that neutralization of IL-10 increases TNF production and mortality, whereas restitution of circulating IL-10 reduces TNF levels and subsequent deleterious effects. Increased plasma levels of IL-10 also have been associated with mortality and disease severity after traumatic injury. IL-10 may significantly contribute to the underlying immunosuppressed state during sepsis through the inhibition and subsequent anergy of immunocytes. For example, IL-10 produced by Th2 cells directly suppresses Th1 cells and can feedback to suppress Th2 cell activity.⁷⁷

Interleukin-12. IL-12 is unique among the cytokines in being the only heterodimeric cytokine. This family, which includes IL-12, IL-23, IL-27, and IL-35, consists of an α -chain that is structurally similar to the IL-6 cytokine and a β -chain that is similar to the class I receptor for cytokines. The individual IL-12 family members are formed from various combinations of the α and β subunits. Despite the sharing of individual subunits and the similarities of their receptors, the IL-12 cytokines have different biologic functions. IL-12 and IL-23 are considered proinflammatory, stimulatory cytokines with key roles in the development of Th1 and Th17 subsets of helper T cells. In contrast, both IL-27 and IL-35 appear to have immunoregulatory functions that are associated with cytokine inhibition in specific Treg cell populations, particularly the Th17 cells.⁷⁸ The effects of these cytokines require specific receptor chains that are also shared among the cytokines. The complexity of signaling is evidenced by the fact that these receptor chains can function both as dimers and as monomers. Ligation of the IL-12 receptors initiates signaling events mediated by the JAK-STAT pathway. IL-12 synthesis and release are increased during endotoxemia and sepsis.⁷⁹ IL-12 stimulates lymphocytes to increase secretion of IFN- γ with the costimulus of IL-18 and also stimulates NK cell cytotoxicity and helper T-cell differentiation in this setting. IL-12 release is inhibited by IL-10. IL-12 deficiency inhibits phagocytosis in neutrophils. In experimental models of inflammatory stress, IL-12 neutralization conferred a mortality benefit in mice during endotoxemia. However, in a cecal ligation and puncture model of intraperitoneal sepsis, IL-12 blockade was associated with increased mortality. Furthermore, later studies of intraperitoneal sepsis observed no difference in mortality with IL-12 administration; however, IL-12 knockout mice exhibited increased bacterial counts and inflammatory cytokine release, which suggests that IL-12 may contribute to an antibacterial response. IL-12 administration in chimpanzees is capable of stimulating the release of proinflammatory mediators such as IFN- γ and also anti-inflammatory mediators, including IL-10, soluble TNFR, and IL-1 receptor antagonists. In addition, IL-12 enhances coagulation as well as fibrinolysis.

Interleukin-18. IL-18 is a member of the IL-1 superfamily of cytokines. First noted as an IFN- γ -inducing factor produced by LPS-stimulated macrophages, IL-18 expression is found both in immune cells and nonimmune cells at low to intermediate levels. However, activated macrophages and Kupffer cells produce large amounts of mature IL-18. Similar to IL-1 β , IL-18 is synthesized and stored as an inactive precursor form (pro-IL-18), and activation requires processing by caspase 1 in response to the appropriate signaling. It then exits the cell through a nontraditional secretory pathway. The IL-18 receptor (IL-18R) is composed of two subunits, IL-18R α and IL-18R β , and is a member of the IL-1R superfamily, which is structurally similar in its cytoplasmic domains to the TLR.

One unique biologic property of IL-18 is the potential, in conjunction with IL-12, to promote the Th1 response to bacterial infection. At the same time, exogenous IL-18 can also enhance the Th2 response and Ig-mediated humoral immunity, as well as augment neutrophil function. Recent studies suggest that IL-18 therapy may hold promise as effective therapy in promoting immune recovery after severe surgical stress.⁸⁰

Interferons. Interferons were first recognized as soluble mediators that inhibited viral replication through the activation of specific antiviral genes in infected cells. Interferons are categorized into three types based on receptor specificity and sequence homology. The two major types, type I and type II, are discussed here.

Type I interferons, of which there are 20, include IFN- α , IFN- β , and IFN- ω , which are structurally related and bind to a common receptor, IFN- α receptor. They are likely produced by most cell types and tissues in response to appropriate pathogens or DAMP signaling. Type I interferons are expressed in response to many stimuli, including viral antigens, double-stranded DNA, bacteria, tumor cells, and LPS. Type I interferons influence adaptive immune responses by inducing the maturation of dendritic cells and by stimulating class I major histocompatibility complex (MHC) expression. IFN- α and IFN- β also enhance immune responses by increasing the cytotoxicity of NK cells both in culture and in vivo. Further, they have been implicated in the enhancement of chemokine synthesis, particularly those that recruit myeloid cells and lymphoid cells. Thus, IFN/STAT signaling has important effects on the mobilization, tissue recruitment, and activation of immune cells that compose the inflammatory infiltrate. In contrast, IFN-I appears to inhibit inflammasome activity, possibly via IL-10.⁸¹

Many of the physiologic effects observed with increased levels of IL-12 and IL-18 are mediated through IFN- γ . IFN- γ is a type II interferon that is secreted by various T cells, NK cells, and antigen-presenting cells in response to bacterial antigens, IL-2, IL-12, and IL-18. IFN- γ stimulates the release of IL-12 and IL-18. Negative regulators of IFN- γ include IL-4, IL-10, and glucocorticoids. IFN- γ binding with a cognate receptor activates the JAK-STAT pathway, leading to subsequent induction of biologic responses. Macrophages stimulated by IFN- γ demonstrate enhanced phagocytosis and microbial killing and increased release of oxygen radicals, partly through an NADP-dependent phagocyte oxidase. IFN- γ mediates macrophage stimulation and thus may contribute to acute lung injury after major surgery or trauma. Diminished IFN- γ level, as seen in knockout mice, is associated with increased susceptibility to both viral and bacterial pathogens. In addition, IFN- γ promotes differentiation of T cells to the helper T-cell subtype 1 and also enhances B-cell isotype switching to immunoglobulin G.⁸²

Receptors of all IFN subtypes belong to the class II of cytokine receptors and use the JAK-STAT signaling pathway for nuclear signaling, although different STAT activation (e.g., STAT1 and STAT2) is favored by individual receptors.

Granulocyte-Macrophage Colony-Stimulating Factor/Interleukin-3/Interleukin-5. GM-CSF, IL-3, and IL-5 compose a small family of cytokines that regulate the growth and activation of immune cells. They are largely the products of activated T cells, which when released stimulate the behavior of myeloid cells by inducing cytokine expression and antigen presentation. In this way, GM-CSF, IL-3, and IL-5 are able to link the innate and acquired immune responses. With the exception

of eosinophils, GM-CSF, IL-3, and IL-5 are not essential for constitutive hematopoietic cell function. Rather, they play an important role when the host is stressed, by serving to increase the numbers of activated and sensitized cells required to bolster host defense.⁸³ Currently, GM-CSF is in clinical trials for administration to children with an Injury Severity Score >10 following blunt or penetrating trauma. The goal of the study is to provide evidence of the effectiveness of GM-CSF as an agent that can ameliorate posttraumatic immune suppression.

Receptors for the GM-CSF/IL-3/IL-5 family of cytokines are expressed at very low levels on hematopoietic cells. Similar to the other cytokine receptors discussed, they are heterodimers composed of a cytokine-specific α subunit and a common β subunit (β_c), which is shared by all three receptors and is required for high-affinity signal transduction. The binding of cytokine to its receptor activates JAK2-STAT-, MAPK-, and PI3K-mediated signaling events to regulate a variety of important cell behaviors including effector function in mature cells.

Eicosanoids

Omega-6 Polyunsaturated Fat Metabolites: Arachidonic Acid. Eicosanoids are derived primarily by oxidation of the membrane phospholipid, **arachidonic acid** [all-*cis*-5,8,11,14-eicosatetraenoic acid; 20:4(ω -6) eicosatetraenoic acid], which

is relatively abundant in the membrane lipids of inflammatory cells. They are composed of three families, which include prostaglandins, thromboxanes, and leukotrienes. Arachidonic acid is not stored free in the cell but in an esterified form in phospholipids and neutral lipids. When a cell senses the proper stimulus, arachidonic acid is released from phospholipids or diacylglycerols by the enzymatic activation of phospholipase A₂ (Fig. 2-6A). Prostanoids, which include all of the prostaglandins and the thromboxanes, result from the sequential action of the cyclooxygenase (COX) enzyme and terminal synthetases on arachidonic acid. In contrast, arachidonic acid may be oxidized along the lipoxygenase pathway via the central enzyme 5-lipoxygenase, to produce several classes of leukotrienes and lipoxins. In general, the effects of eicosanoids are mediated via specific receptors, which are members of a superfamily of G-protein-coupled receptors.

Eicosanoids are not stored within cells but are instead generated rapidly in response to many stimuli, including hypoxic injury, direct tissue injury, endotoxin (lipopolysaccharide), NE, vasopressin, angiotensin II, bradykinin, serotonin, ACh, cytokines, and histamine. Eicosanoid pathway activation also leads to the formation of the anti-inflammatory compound lipoxin, which inhibits chemotaxis and NF- κ B activation. Glucocorticoids, nonsteroidal anti-inflammatory drugs, and leukotriene

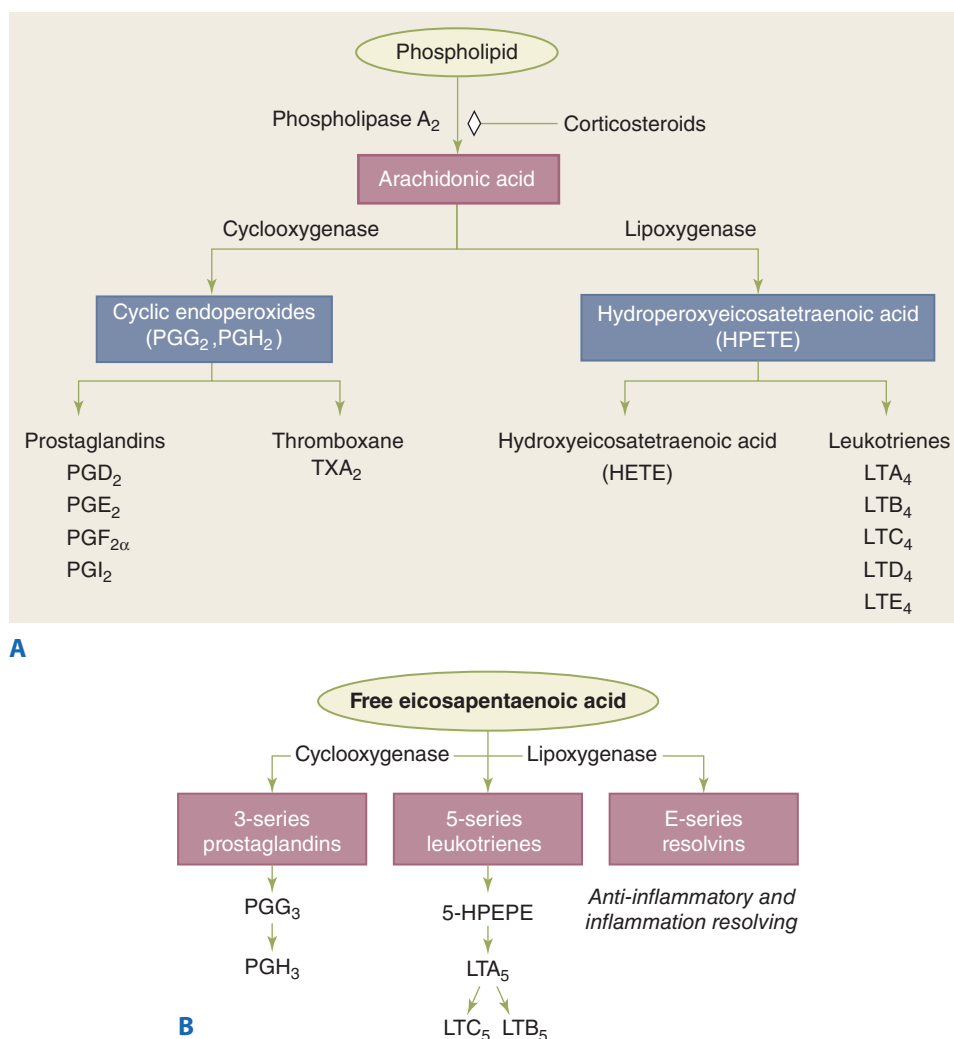


Figure 2-6. Schematic diagram of (A) arachidonic acid and (B) eicosapentaenoic acid metabolism. LT = leukotriene; PG = prostaglandin; TXA₂ = thromboxane A₂; HPEPE = hydroperoxyeicosapentaenoic acid.

inhibitors block the end products of eicosanoid pathways. Eicosanoids have a broad range of physiologic roles, including neurotransmission and vasomotor regulation. They are also involved in immune cell regulation (Table 2-6) by modulating the intensity and duration of inflammatory responses. The production of eicosanoids is cell- and stimulus-specific. Therefore, the signaling events that are initiated will depend on the concentrations and types of eicosanoids generated, as well as the unique complement of receptors expressed by their target cells. For example, prostaglandin E_2 (PGE_2) suppresses the effector function of macrophages (i.e., phagocytosis and intracellular pathogen killing) via a mechanism that is dependent on increased cAMP levels. PGE_2 also modulates chemokine

TABLE 2-6

Systemic stimulatory and inhibitory actions of eicosanoids

ORGAN/FUNCTION	STIMULATOR	INHIBITOR
<i>Pancreas</i>		
Glucose-stimulated insulin secretion	12-HPETE	PGE_2
Glucagon secretion	PGD_2 , PGE_2	
<i>Liver</i>		
Glucagon-stimulated glucose production		PGE_2
<i>Fat</i>		
Hormone-stimulated lipolysis		PGE_2
<i>Bone</i>		
Resorption	PGE_2 , PGE -m, 6-K- PGE_1 , $PGF_{1\alpha}$, PGI_2	
<i>Pituitary</i>		
Prolactin	PGE_1	
Luteinizing hormone	PGE_1 , PGE_2 , 5-HETE	
Thyroid-stimulating hormone	PGA_1 , PGB_1 , PGE_1 , PGE_1	
Growth hormone	PGE_1	
<i>Parathyroid</i>		
Parathyroid hormone	PGE_2	PGF_2
<i>Lung</i>		
Bronchoconstriction	$PGF_{2\alpha}$, TXA_2 , LTC_4 , LTD_4 , LTE_4	PGE_2
<i>Kidney</i>		
Stimulation of renin secretion	PGE_2 , PGI_2	
<i>Gastrointestinal system</i>		
Cytoprotective effect	PGE_2	
<i>Immune response</i>		
Suppression of lymphocyte activity	PGE_2	
<i>Hematologic system</i>		
Platelet aggregation	TXA_2	PGI_2

5-HETE = 5-hydroxyeicosatetraenoic acid; 12-HPETE = 12-hydroxyperoxyeicosatetraenoic acid; 6-K- PGE_1 = 6-keto-prostaglandin E_1 ; LT = leukotriene; PG = prostaglandin; PGE -m = 13,14-dihydro-15-keto- PGE_2 (major urine metabolite of PGE_2); TXA_2 = thromboxane A_2 .

production and enhances local accumulation of regulatory T cells and myeloid-derived suppressor cells. Prostacyclin (PGI_2) has an inhibitory effect on Th1- and Th2-mediated immune responses, while enhancing Th17 differentiation and cytokine production. Leukotrienes are potent mediators of capillary leakage as well as leukocyte adherence, neutrophil activation, bronchoconstriction, and vasoconstriction. Leukotriene B_4 is synthesized from arachidonic acid in response to acute Ca^{2+} signaling induced by inflammatory mediators.⁸⁴ High-affinity leukotriene receptors (BLT1) are expressed primarily in leukocytes, including granulocytes, eosinophils, macrophages, and differentiated T cells, whereas the low-affinity receptor is expressed in many cell types. Activation of BLT1 results in inhibition of adenylate cyclase and reduced production of cAMP. Not surprisingly, a role for leukotriene B_4 signaling in abrogating the effects of prostaglandins on macrophage effector function has recently been shown.⁸⁵

Recent evidence supports a role for **lipid droplets** (LDs) as an important intracellular source of arachidonic acid. LDs are neutral lipid storage organelles ubiquitous to eukaryotic cells that are a rich source of esterified arachidonic acid especially in leukocytes. Accumulation of LDs in response to TLR signaling has been reported with an associated increase in the generation of eicosanoid metabolites.⁸⁶

While experimental models of sepsis have shown a benefit to inhibiting eicosanoid production, human sepsis trials have failed to show a mortality benefit.⁸⁷ Eicosanoids also have several recognized metabolic effects. COX pathway products inhibit pancreatic β -cell release of insulin, whereas lipoxygenase pathway products stimulate β -cell activity. Prostaglandins such as PGE_2 can inhibit gluconeogenesis through the binding of hepatic receptors and also can inhibit hormone-stimulated lipolysis.⁸⁸

Omega-3 Polyunsaturated Fat Metabolites: All-*cis*-5,8,11,14,17-Eicosapentaenoic Acid [20:5(ω -3) Eicosapentaenoic Acid]. As noted earlier, polyunsaturated fatty acid (PUFA) metabolites of endogenous arachidonic acid function as inflammatory mediators and have significant roles in the inflammatory response. The major direct dietary source of arachidonic acid is from meat. However, a much larger quantity of ω -6 PUFAs is ingested as linoleic acid, which is found in many vegetable oils, including corn, sunflower, and soybean oils, and in products made from such oils, such as margarines. Linolenic acid is not synthesized in mammals; however, it can be converted to arachidonic acid through lengthening of the carbon chain and the addition of double bonds. The second major family of PUFAs is the ω -3 fatty acid. They can also be derived from shorter chain ω -3 fatty acids of plant origin such as α -linolenic acid, which can be converted after ingestion to eicosapentaenoic acid (EPA) and to docosahexaenoic acid (DHA). ω -3 fatty acids are found in cold water fish, especially tuna, salmon, mackerel, herring, and sardine, which can provide between 1.5 and 3.5 g of these long-chain ω -3 PUFAs per serving. EPA and DHA are also substrates for the COX and lipoxygenase (LOX) enzymes that produce eicosanoids, but the mediators produced have a different structure from the arachidonic acid-derived mediators, and this influences their potency (Fig. 2-6B). In addition, ω -3 fatty acids are reported to have specific anti-inflammatory effects, including inhibition of NF- κ B activity, TNF release from hepatic Kupffer cells, and leukocyte adhesion and migration. These are achieved via two purported mechanisms: (a) by decreasing the production of arachidonic

acid (ω -6)–derived proinflammatory mediators (by competition for the same enzymes) and (b) by generation of proresolving bioactive lipid mediators. In fact, key derivatives of ω -3 PUFAs, termed resolvins, have been identified and synthesized. Resolvins are now categorized as either E-series (from EPA) or D-series (from DHA). In a variety of model systems, resolvins have been shown to attenuate the inflammatory phenotypes of a number of immune cells.⁸⁹

The ratio of dietary ω -6 to ω -3 PUFAs is reflected in the membrane composition of various cells, including cells of the immune system, which has potential implications for the inflammatory response. For example, a diet that is rich in ω -6 PUFAs will result in cells whose membranes are “ ω -6 PUFA rich.” When ω -6 PUFAs are the main plasma membrane lipid available for phospholipase activity, more proinflammatory PUFAs (i.e., two-series prostaglandins) are generated. Many lipid preparations are soy-based and thus primarily composed of ω -6 fatty acids. These are thought to be “inflammation enhancing.” Nutritional supplementation with ω -3 fatty acid has the potential to dampen inflammation by shifting the cell membrane composition in favor of ω -3 PUFAs.

In experimental models of sepsis, ω -3 fatty acids inhibit inflammation, ameliorate weight loss, increase small-bowel perfusion, and may increase gut barrier protection. In human studies, ω -3 supplementation is associated with decreased production of TNF, IL-1 β , and IL-6 by endotoxin-stimulated monocytes. In a study of surgical patients, preoperative supplementation with ω -3 fatty acid was associated with reduced need for mechanical ventilation, decreased hospital length of stay, and decreased mortality with a good safety profile.⁹⁰

Plasma Contact System

Complement. Following traumatic injury, there is almost immediate activation of the complement system, which is a major effector mechanism of the innate immune system. The complement system was thought to act initially as the required “first line of defense” for the host against pathogens, by binding and clearing them from the circulation. Recent data indicate that complement also participates in the elimination of immune complexes as well as damaged and dead cells. In addition, complement is recognized as contributing to mobilization of hematopoietic stem/progenitor cells and lipid metabolism.⁹¹ Although complement activation is typically depicted as a linear process in which parallel pathways are activated, it actually functions more like a central node that is tightly networked with other systems. Then, depending on the activating signal, several initiation and regulatory events act in concert to heighten immune surveillance.

Complement activation proceeds via three different pathways. Initiation of these pathways occurs by the binding and activation of the recognition unit of each pathway to its designated ligand. The classical pathway, which is often referred to as “antibody dependent,” is initiated by direct binding of C1q to its common ligands, which include immunoglobulin (Ig) M/IgG aggregates. Alternately C1q can activate complement signaling by binding to soluble pattern recognition molecules such as pentraxins (e.g., CRP). In a series of subsequent activation and amplification steps, the pathway ultimately leads to the assembly of the C3 convertase, which cleaves C3 into C3a and C3b. As C3b then complexes with C3 convertase, the C5 convertase is activated, cleaving C5 into C5a and C5b. C3a and C5a are potent anaphylatoxins. C3b acts as an opsonin, whereas C5b initiates the formation of the membrane attack complex. When C5b

associates with C6 and C7, the complex becomes inserted into cell membrane and interacts with C8, inducing the binding of several units of C9 to form a lytic pore.

The lectin pathway of complement activation is initiated by mannose-binding lectins or ficolins, which act as the soluble PRM by binding specific carbohydrate structures that are often present on pathogens. The alternative pathway also includes a PRM-based initiation mechanism that resembles those found in the lectin pathway but involves properdin. The latter recognizes several PAMPs and DAMPs on foreign and apoptotic cells. Once bound, it initiates and propagates the complement response by attracting fluid-phase C3b to recognized surfaces and by stabilizing C3 convertase complexes. Despite its name, the alternative pathway may account for up to 80% to 90% of total complement activation.⁹²

The major source of the circulating complement components is the liver. Complement proteins can also be produced locally where they have been implicated in the regulation of adaptive immune processes. Complement protein synthesis has been demonstrated in immune cells, including T cells, which when surface bound, interact with C3 and C4 receptors. Also, complement synergistically enhances TLR-induced production of proinflammatory cytokines through convergence of their signaling pathways.

Kallikrein-Kinin System. The kallikrein-kinin system is a group of proteins that contribute to inflammation, blood pressure control, coagulation, and pain responses. Prekallikrein is synthesized in the liver and circulates in the plasma bound to high molecular weight kininogen (HK). A variety of stimuli lead to the binding of prekallikrein-HK complex to Hageman factor, (factor XII) followed by its activation, to produce the serine protease **kallikrein**, which plays a role in the coagulation cascade. HK, produced by the liver, is cleaved by kallikrein to form bradykinin (BK). The **kinins** (e.g., BK) mediate several physiologic processes, including vasodilation, increased capillary permeability, tissue edema, pain pathway activation, inhibition of gluconeogenesis, and increased bronchoconstriction. They also increase renal vasodilation and consequently reduce renal perfusion pressure. Kinin receptors are members of the rhodopsin family of G-protein–coupled receptors and are located on vascular endothelium and smooth muscle cells. Kinin receptors are rapidly upregulated following TLR4 signaling and in response to cytokines and appear to have important effects on both immune cell behavior and on immune mediators.⁹³ For example, B1 activation results in increased neutrophil chemotaxis, while increased B2 receptor expression causes activation of arachidonic-prostaglandin pathways. Bradykinin and kallikrein levels are increased during gram-negative bacteremia, hypotension, hemorrhage, endotoxemia, and tissue injury. The degree of elevation in the levels of these mediators has been associated with the magnitude of injury and mortality. Clinical trials using bradykinin antagonists have shown some benefit in patients with gram-negative sepsis.⁹⁴

Serotonin

Serotonin is a monoamine neurotransmitter (5-hydroxytryptamine [5-HT]) derived from tryptophan. Serotonin is synthesized by neurons in the CNS as well as by intestinal enterochromaffin cells, which are the major source of plasma 5-HT. Once in the plasma, 5-HT is taken up rapidly into platelets via the serotonin transporter (SERT) where it is either stored in the dense granules in millimolar concentrations or targeted for degradation. It is

interesting that the surface expression of SERT on platelets is sensitive to plasma 5-HT levels, which in turn modulates platelet 5-HT content. Receptors for serotonin are widely distributed in the periphery and are found in the gastrointestinal tract, cardiovascular system, and some immune cells.⁹⁵ Serotonin is a potent vasoconstrictor and also modulates cardiac inotropy and chronotropy through nonadrenergic cAMP pathways. Serotonin is released at sites of injury, primarily by platelets. Recent work has demonstrated an important role for platelet 5-HT in the local inflammatory response to injury. Using mice that lack the non-neuronal isoform of tryptophan hydroxylase (Tph1), the rate-limiting step for 5-HT synthesis in the periphery, investigators demonstrated fewer neutrophils rolling on mesenteric venules.⁹⁶ Tph1^{-/-} mice, in response to an inflammatory stimulus, also showed decreased neutrophil extravasation. Finally, survival of lipopolysaccharide-induced endotoxic shock was reduced in Tph1^{-/-} mice. Together, these data indicate an important role for nonneuronal 5-HT in neutrophil recruitment to sites inflammation and injury.

Histamine

Histamine is a short-acting endogenous amine that is widely distributed throughout the body. It is synthesized by histidine decarboxylase (HDC), which decarboxylates the amino acid histidine. Histamine is either rapidly released or stored in neurons, skin, gastric mucosa, mast cells, basophils, and platelets, and plasma levels are increased with hemorrhagic shock, trauma, thermal injury, and sepsis.⁹⁷ Not surprisingly, circulating cytokines can increase immune cell expression of HDC to further contribute to histamine synthesis. There are four histamine receptor (HR) subtypes with varying physiologic roles, but they are all members of the rhodopsin family of G-protein-coupled receptors. H1R binding mediates vasodilation, bronchoconstriction, intestinal motility, and myocardial contractility. H1R knockout mice demonstrate significant immunologic defects, including impaired B- and T-cell responses. H2R binding is best described for its stimulation of gastric parietal cell acid secretion. However, H2R can also modulate a range of immune system activities, such as mast cell degranulation, antibody synthesis, Th1 cytokine production, and T-cell proliferation. H3R was initially classified as a presynaptic autoreceptor in the peripheral nervous system and CNS. However, data using H3R knockout mice demonstrate that it also participates in inflammation in the CNS. H3R knockout mice display increased severity of neuroinflammatory diseases, which correlates with dysregulation of blood-brain barrier permeability and increased expression of macrophage inflammatory protein 2, IFN-inducible protein 10, and CXCR3 by peripheral T cells. H4R is expressed primarily in bone marrow but has also been detected in leukocytes, including neutrophils, eosinophils, mast cells, dendritic cells, T cells, and basophils. H4R is emerging as an important modulator of chemoattraction and cytokine production in these cells. Thus, it is clear that cells of both the innate and adaptive immune response can be regulated by histamine, which is upregulated following injury.⁹⁸

CELLULAR RESPONSE TO INJURY

Cytokine Receptor Families and Their Signaling Pathways

Cytokines act on their target cells by binding to specific membrane receptors. These receptor families have been organized

by structural motifs and include: type I cytokine receptors, type II cytokine receptors, chemokine receptors, TNF receptors (TNFRs), and transforming growth factor receptors (TGFs). In addition, there are cytokine receptors that belong to the immunoglobulin receptor superfamilies. Several of these receptors have characteristic signaling pathways that are associated with them. These will be reviewed in the following sections.

JAK-STAT Signaling

A major subgroup of cytokines, comprising roughly 60 factors, bind to receptors termed type I/II cytokine receptors. Cytokines that bind these receptors include type I IFNs, IFN- γ , many ILs (e.g., IL-6, IL-10, IL-12, and IL-13), and hematopoietic growth factors. These cytokines play essential roles in the initiation, maintenance, and modulation of innate and adaptive immunity for host defense. All type I/II cytokine receptors selectively associate with the Janus kinases (JAKs), which represent a family of tyrosine kinases that mediate the signal transduction for these receptors. JAKs are constitutively bound to the cytokine receptors, and on ligand binding and receptor dimerization, activated JAKs phosphorylate the receptor to recruit signal transducer and activator of transcription (STAT) molecules (Fig. 2-7). Activated STAT proteins further dimerize and translocate into

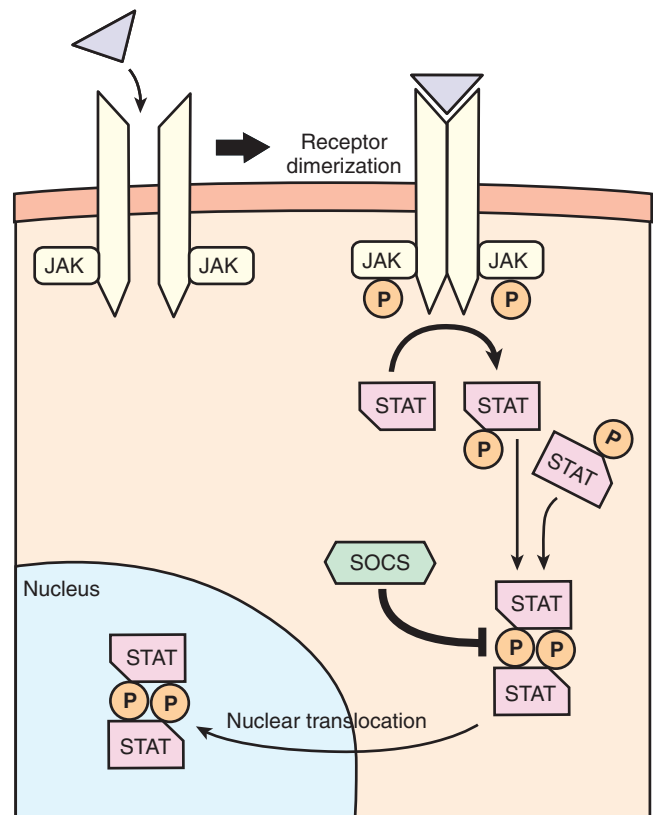


Figure 2-7. The Janus kinase/signal transducer and activator of transcription (JAK/STAT) signaling pathway also requires dimerization of monomeric units. STAT molecules possess “docking” sites that allow for STAT dimerization. The STAT complexes translocate into the nucleus and serve as gene transcription factors. JAK/STAT activation occurs in response to cytokines (e.g., interleukin-6) and cell stressors, and has been found to induce cell proliferation and inflammatory function. Intracellular molecules that inhibit STAT function, known as *suppressors of cytokine signaling* (SOCSs), have been identified. P = phosphate.

the nucleus where they modulate the transcription of target genes. Rather than being a strictly linear pathway, it is likely that individual cytokines activate more than one STAT. The molecular implications for this in terms of cytokine signaling are still being unraveled. Interestingly, STAT-DNA binding can be observed within minutes of cytokine binding. STATs have also been shown to modulate gene transcription via epigenetic mechanisms. Thus, JAKs and STATs are central players in the regulation of key immune cell function, by providing a signaling platform for proinflammatory cytokines (IL-6 via JAK1 and STAT3) and anti-inflammatory cytokines (IL-10 via STAT3) and integrating signals required for helper and regulatory T-cell development and differentiation. The JAK/STAT pathway is inhibited by the action of phosphatase, the export of STATs from the nucleus, and the interaction of antagonistic proteins.⁹⁹

Suppressors of Cytokine Signaling

Suppressor of cytokine signaling (SOCS) molecules are a family of proteins that function as a negative feedback loop for type I and II cytokine receptors by terminating JAK-STAT signaling. There are currently eight family members; SOCS1-3 are typically associated with cytokine receptor signaling, whereas SOCS4-8 are associated with growth factor receptor signaling. PRRs, including both TLR and C-type lectin receptors, have also been shown to activate SOCS. Interestingly, induction of SOCS proteins is also achieved through activators of JAK-STAT signaling, creating an inhibitory feedback loop through which cytokines can effectively self-regulate by extinguishing their own signal. SOCS molecules can positively and negatively influence the activation of macrophages and dendritic cells and are crucial for T-cell development and differentiation. All SOCS proteins are able to regulate receptor signaling through the recruitment of proteasomal degradation components to their target proteins,

whether the target is a specific receptor or an associated adaptor molecule. Once associated with the SOCS complex, target proteins are readily ubiquitinated and targeted to the proteasome for degradation. SOCS1 and SOCS3 can also exert an inhibitory effect on JAK-STAT signaling via their N-terminal kinase inhibitory region (KIR) domain, which acts as a pseudosubstrate for JAK. The KIR domain binds with high affinity to the JAK kinase domain to inhibit its activity. SOCS3 has been shown to be a positive regulator of TLR4 responses in macrophages via inhibition of IL-6 receptor-mediated STAT3 activation.¹⁰⁰ A deficiency of SOCS activity may render a cell hypersensitive to certain stimuli, such as inflammatory cytokines and GHs. Interestingly, in a murine model, SOCS knockout resulted in a lethal phenotype in part because of unregulated interferon signaling.

Chemokine Receptors Are Members of the G-Protein–Coupled Receptor Family

All chemokine receptors are members of the G-protein–coupled seven-transmembrane family of receptors (GPCR), which is one of the largest and most diverse of the membrane protein families. GPCRs function by detecting a wide spectrum of extracellular signals, including photons, ions, small organic molecules, and entire proteins. After ligand binding, GPCRs undergo conformational changes, causing the recruitment of heterotrimeric G proteins to the cytoplasmic surface (Fig. 2-8). Heterotrimeric G proteins are composed of three subunits, $G\alpha$, $G\beta$, and $G\gamma$, each of which has numerous members, adding to the complexity of the signaling. When signaling however, G proteins perform functionally as dimers because the signal is communicated either by the $G\alpha$ subunit or the $G\beta\gamma$ complex. The GPCR family includes the receptors for catecholamines, bradykinins, and leukotrienes, in addition to a variety of other ligands important to the inflammatory response.¹⁰¹ In general, GPCRs can

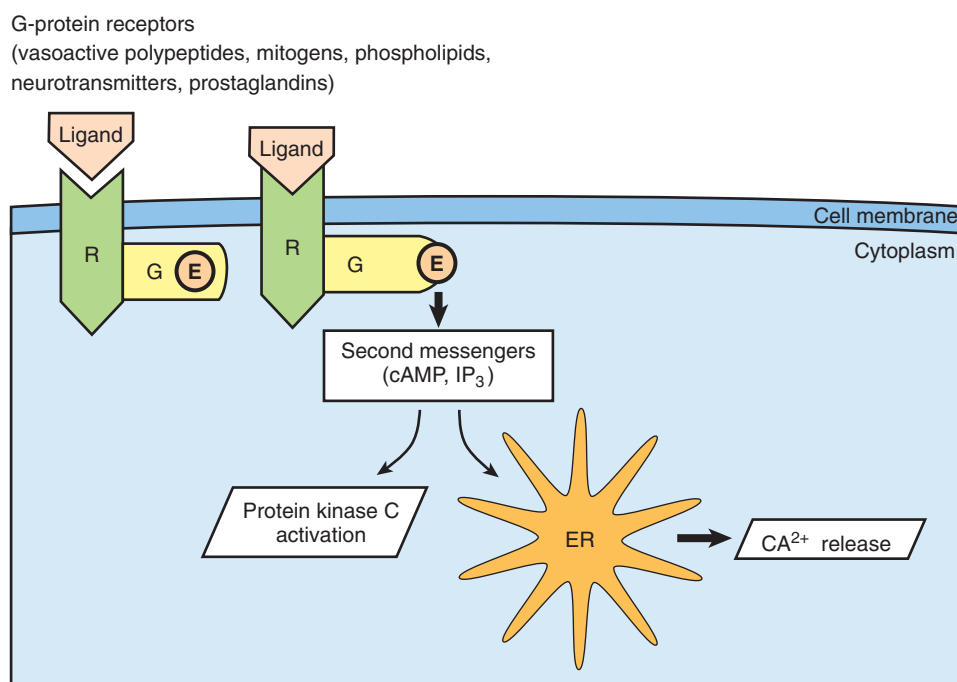


Figure 2-8. G-protein–coupled receptors are transmembrane proteins. The G-protein receptors respond to ligands such as adrenaline and serotonin. On ligand binding to the receptor (R), the G protein (G) undergoes a conformational change through guanosine triphosphate–guanosine diphosphate conversion and in turn activates the effector (E) component. The E component subsequently activates second messengers. The role of inositol triphosphate (IP₃) is to induce release of calcium from the endoplasmic reticulum (ER). cAMP = cyclic adenosine triphosphate.

be classified according to their pharmacologic properties into four main families: class A rhodopsin-like, class B secretin-like, class C metabotropic glutamate/pheromone, and class D frizzled receptors. As noted earlier, GPCR activation by ligand binding results in an extracellular domain shift, which is then transmitted to cytoplasmic portion of the receptor to facilitate coupling to its principle effector molecules, the heterotrimeric G proteins. Although there are more than 20 known $G\alpha$ subunits, they have been divided into four families based on sequence similarity, which has served to define both receptor and effector coupling. These include $G\alpha_s$ and $G\alpha_i$, which signal through the activation ($G\alpha_s$) or inhibition ($G\alpha_i$) of adenylate cyclase to increase or decrease cAMP levels, respectively. Increased intracellular cAMP can activate gene transcription through the activity of intracellular signal transducers such as protein kinase A. The $G\alpha$ subunits also include the G_q pathway, which stimulates phospholipase C- β to produce the intracellular messengers inositol triphosphate and diacylglycerol. Inositol triphosphate triggers the release of **calcium** from intracellular stores, whereas diacylglycerol recruits protein kinase C to the plasma membrane for activation. Finally, $G\alpha_{12/13}$ appears to act through Rho- and Ras-mediated signaling.

Tumor Necrosis Factor Superfamily

The signaling pathway for TNFR1 (55 kDa) and TNFR2 (75 kDa) occurs by the recruitment of several adapter proteins to the intracellular receptor complex. Optimal signaling activity requires receptor trimerization. TNFR1 initially recruits TNFR-associated death domain (TRADD) and induces apoptosis through the actions of proteolytic enzymes known as *caspases*, a pathway shared by another receptor known as *CD95 (Fas)*. CD95 and TNFR1 possess similar intracellular sequences known as *death domains (DDs)*, and both recruit the same adapter proteins known as *Fas-associated death domains (FADDs)* before activating caspase 8. TNFR1 also induces apoptosis by activating caspase 2 through the recruitment of receptor-interacting protein (RIP). RIP also has a functional component that can initiate NF- κ B and c-Jun activation, both favoring cell survival and proinflammatory functions. TNFR2 lacks a DD component but recruits adapter proteins known as TNFR-associated factors 1 and 2 (TRAF1, TRAF2) that interact with RIP to mediate NF- κ B and c-Jun activation. TRAF2 also recruits additional proteins that are antiapoptotic, known as inhibitor of apoptosis proteins (IAPs).

Transforming Growth Factor- β Family of Receptors

Transforming growth factor- β 1 (TGF- β 1) is a pleiotropic cytokine expressed by immune cells that has potent immunoregulatory activities. Specifically, recent data indicate that TGF- β is essential for T-cell homeostasis, as mice deficient in TGF- β 1 develop a multiorgan autoimmune inflammatory disease and die a few weeks after birth, an effect that is dependent on the presence of mature T cells. The receptors for TGF- β ligands are the TGF- β superfamily of receptors, which are type I transmembrane proteins that contain intrinsic serine/threonine kinase activity. These receptors comprise two subfamilies, the type I and the type II receptors, which are distinguished by the presence of a glycine/serine-rich membrane domain found in the type I receptors. Each TGF- β ligand binds a characteristic combination of type I and type II receptors, both of which are required for signaling. Whether the type I or the type II receptor

binds first is ligand-dependent, and the second type I or type II receptor is then recruited to form a heteromeric signaling complex. When TGF- β binds to the TGF- β receptor, heterodimerization activates the receptor, which then directly recruits and activates a receptor-associated Smad (Smad2 or Smad3) through phosphorylation. An additional “common” Smad is then recruited. The activated Smad complex translocates into the nucleus and, with other nuclear cofactors, regulates the transcription of target genes. TGF- β can also induce the rapid activation of the Ras-extracellular signal-regulated kinase (ERK) signaling pathway in addition to other MAPK pathways (JNK, p38MAPK). How does TGF- β inhibit immune responses? One of the most important effects is the suppression of IL-2 production by T cells. It also inhibits T-cell proliferation.¹⁰² More recently, it was noted that TGF- β can regulate the maturation of differentiated dendritic cells and dendritic cell-mediated T-cell responses. Importantly, TGF- β can induce “alternative activation” macrophages, designated M2 macrophages, which express a wide array of anti-inflammatory molecules, including IL-10 and arginase-1.

5 ▶ TRANSCRIPTIONAL AND TRANSLATIONAL REGULATION OF THE INJURY RESPONSE

Transcriptional Events Following Blunt Trauma

Recent data have examined the transcriptional response in circulating leukocytes in a large series of patients who suffered severe blunt trauma. This work identified an overwhelming shift in the leukocyte transcriptome, with more than 80% of the cellular functions and pathways demonstrating some alteration in gene expression. In particular, changes in gene expression for pathways involved in the systemic inflammatory, innate immune, compensatory anti-inflammatory, and adaptive immune responses were simultaneous and marked. Moreover, they occurred rapidly (within 4 to 12 hours) and were prolonged for days and weeks. When different injuries (i.e., blunt trauma, burn injury, human model of endotoxemia) were compared, the patterns of gene expression were surprisingly similar, suggesting that the stress response to both injury and inflammation is highly conserved and may follow a universal pathway that includes common denominators. Finally, delayed clinical recovery and organ injury were not associated with a distinct pattern of transcriptional response elements.² These data describe a new paradigm based on the observation of a rapid and coordinated transcriptional response to severe traumatic injury that involves both the innate and adaptive immune systems. Further, the data support the idea that individuals who are destined to die from their injuries are characterized primarily by the degree and duration of their dysregulated inflammatory response rather than a “unique signature” indicative of a “second hit.”

Transcriptional Regulation of Gene Expression

Many genes are regulated at the point of DNA transcription and thus influence whether messenger RNA (mRNA) and its subsequent product are expressed (Fig. 2-9). Gene expression relies on the coordinated action of transcription factors and coactivators (i.e., regulatory proteins), which are complexes that bind to highly specific DNA sequences upstream of the target gene known as the *promoter region*. Enhancer sequences of DNA mediate gene expression, whereas repressor sequences are non-coding regions that bind proteins to inhibit gene expression.

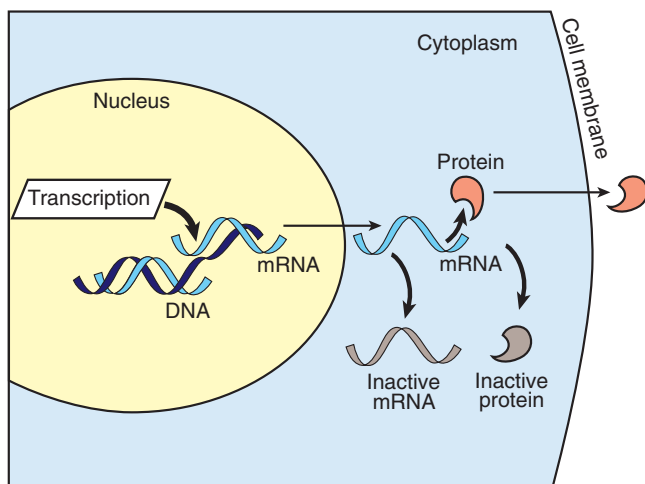


Figure 2-9. Gene expression and protein synthesis can occur within a 24-hour period. The process can be regulated at various stages: transcription, messenger RNA (mRNA) processing, or protein packaging. At each stage, it is possible to inactivate the mRNA or protein, rendering these molecules nonfunctional.

For example, NF- κ B is one of the best-described transcription factors, which has a central role in regulating the gene products expressed after inflammatory stimuli (Fig. 2-10). NF- κ B is composed of two smaller polypeptides, p50 and p65. NF- κ B resides in the cytosol in the resting state primarily through the inhibitory binding of inhibitor of κ B (I- κ B). In response to an inflammatory stimulus such as TNF, IL-1, or endotoxin, a sequence of intracellular mediator phosphorylation reactions leads to the degradation of I- κ B and subsequent release of NF- κ B. On release, NF- κ B travels to the nucleus and promotes gene expression. NF- κ B also stimulates the gene expression for I- κ B, which results in negative feedback regulation. In clinical

appendicitis, for example, increased NF- κ B activity was associated with initial disease severity, and levels returned to baseline within 18 hours after appendectomy in concert with resolution of the inflammatory response.³⁰

Epigenetic Regulation of Transcription

The DNA access of protein machineries involved in transcription processes is tightly regulated by **histones**, which are a family of basic proteins that associate with DNA in the nucleus. Histone proteins help to condense the DNA into tightly packed nucleosomes that limit transcription. Emerging evidence indicates that transcriptional activation of many proinflammatory genes requires nucleosome remodeling that is modulated by the post-translational modification of histone proteins through the recruitment of histone-modifying enzymes.¹⁰³ There are at least seven identified chromatin modifications including acetylation, methylation, phosphorylation, ubiquitinylation, sumoylation, ADP ribosylation, deimination, and proline isomerization. Recently, the development of chromatin immunoprecipitation (ChIP) coupled to massively parallel DNA sequencing technology (ChIP-Seq) has enabled the mapping of histone modifications in living cells in response to TLR signaling. In this way, it has allowed the identification of the large number of posttranslational histone modifications that are “written” and “erased” by histone-modifying enzymes. The role of histone modifications in the regulation of gene expression is referred to as “epigenetic” control.

Addition of an acetyl group to lysine residues on histones is an epigenetic mark associated with gene activation. These acetyl groups are reversibly maintained by **histone acetyltransferases (HATs)** and **histone deacetylases**. Ultimately, histone acetylation is monitored by bromodomain-containing proteins such as the bromodomain and extraterminal domain (BET) family of proteins, which can regulate a number of important epigenetically controlled processes.

Upon TLR4 activation, HATs are recruited to proinflammatory gene promoters where acetylation of specific histone

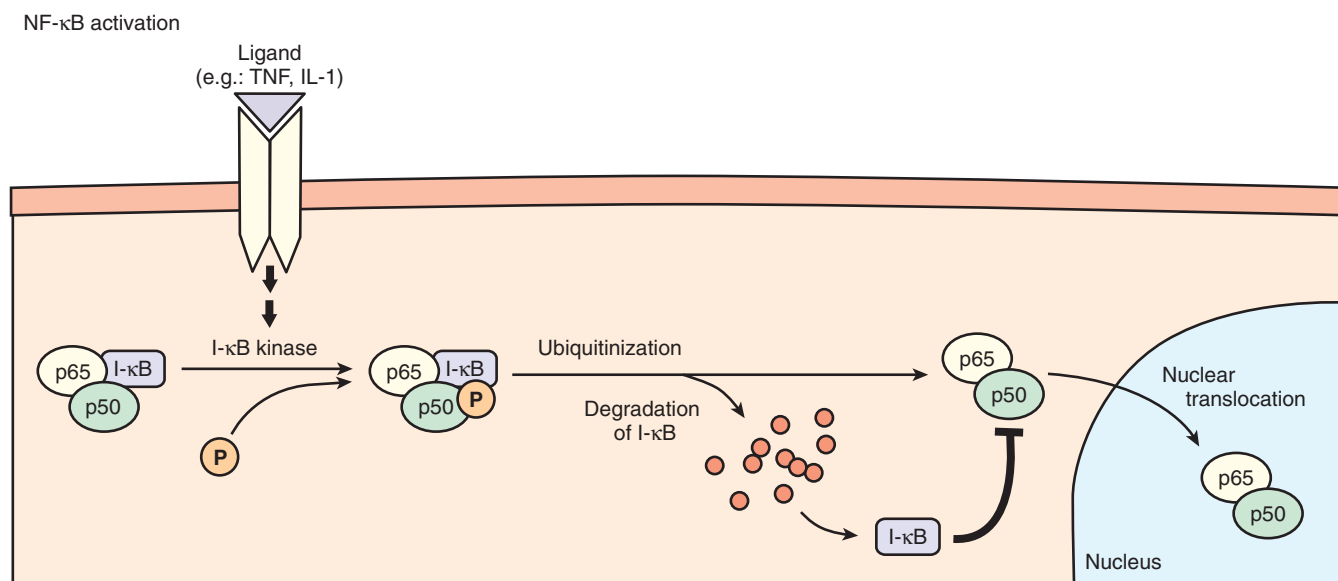


Figure 2-10. Inhibitor of κ B (I- κ B) binding to the p50-p65 subunits of nuclear factor κ B (NF- κ B) inactivates the molecule. Ligand binding to the receptor activates a series of downstream signaling molecules, of which I- κ B kinase is one. The phosphorylated NF- κ B complex further undergoes ubiquitination and proteasome degradation of I- κ B, activating NF- κ B, which translocates into the nucleus. Rapid resynthesis of I- κ B is one method of inactivating the p50-p65 complex. IL-1 = interleukin-1; P = phosphate; TNF = tumor necrosis factor.

residues serves as an organizing node for a complex of proteins that ultimately phosphorylate the large subunit of RNA polymerase II, promoting the elongation of inflammatory gene transcripts.¹⁰⁴ Recently, investigators used a novel pharmacologic approach that targeted inflammatory gene expression by interfering with the recognition of acetylated histones by BET proteins. A synthetic compound (I-BET) that “mimicked” acetylated histones functioned as a BET antagonist.¹⁰⁵ In this way, pretreatment decreased overall histone acetylation to reduce the expression of select inflammatory genes in LPS-activated macrophages. Additionally, I-BET conferred protection against bacteria-induced sepsis. Recent studies have also demonstrated a role for histone methyltransferases in proinflammatory gene programs.

Translation Regulation of Inflammatory Gene Expression

Once mRNA transcripts are generated, they can also be regulated by a variety of mechanisms, including (a) splicing, which can cleave mRNA and remove noncoding regions; (b) capping, which modifies the 5′ ends of the mRNA sequence to inhibit breakdown by exonucleases; and (c) the addition of a polyadenylated tail, which adds a noncoding sequence to the mRNA, to regulate the half-life of the transcript. Recent data have identified microRNAs (miRNAs) as important **translational regulators** of gene expression via their binding to partially complementary sequences in the 3′-untranslated region (3′-UTR) of target mRNA transcripts.¹⁰⁶ Binding of miRNA to the mRNA usually results in gene silencing. MicroRNAs are endogenous, single-stranded RNAs of approximately 22 nucleotides in length that are highly conserved in eukaryotes. miRNAs are encoded either singly or can be transcribed in “polycistronic” clusters and produced by an elaborate expression and processing mechanism. After a primary miRNA transcript is generated by RNA polymerase II or III, it is processed in the nucleus to produce a short hairpin precursor miRNA transcript. The precursor is then transported into the cytoplasm where the final mature miRNA is generated by a protein termed **Dicer**. The mature double-stranded miRNA is then incorporated into the RNA-induced silencing complex (**RISC**) in the cytoplasm. Once programmed with a small RNA, RISC can silence targeted genes by one of several distinct mechanisms, working at (a) the level of protein synthesis through translation inhibition, (b) the transcript level through mRNA degradation, or (c) the level of the genome itself through the formation of heterochromatin or by DNA elimination. Recent data indicate that miRNAs are involved in TLR signaling in the innate immune system by targeting multiple molecules in the TLR signaling pathways.¹⁰⁷ For example, evidence has shown that miR-146a can inhibit the expression of IRAK1 and TRAF6, impair NF-κB activity, and suppress the expression of NF-κB target genes such as IL-6, IL-8, IL-1β, and TNF-α.

CELL-MEDIATED INFLAMMATORY RESPONSE

Platelets

Platelets are small (2 μm), circulating fragments of a larger cell precursor, the megakaryocyte, that is located chiefly within the bone marrow. Although platelets lack a nucleus, they contain both mRNA and a large number of cytoplasmic and surface proteins that equip them for diverse functionality. While their role in hemostasis is well described, more recent work suggests that

platelets play a role in both local and systemic inflammatory responses, particularly following ischemia reperfusion. Platelets express functional scavenger and TLRs that are important detectors of both pathogens and “damage”-associated molecules.¹⁰⁸ At the site of tissue injury, complex interactions between platelets, endothelial cells, and circulating leukocytes facilitate cellular activation by the numerous local alarmins and immune mediators. For example, platelet-specific TLR4 activation can cause thrombocytes to bind to and activate neutrophils to extrude their DNA to form neutrophil extracellular traps (**NETs**), an action that facilitates the capacity of the innate immune system to trap bacteria, but also leads to local endothelial cell damage.¹⁰⁹

Once activated, platelets adopt an initial proinflammatory phenotype by expressing and releasing a variety of adhesion molecules, cytokines, and other immune modulators, including HMGB1, IL-1β, and CD40 ligand (CD40L; CD154). However, activated platelets also express large amounts of the immunosuppressive factor TGF-β, which has been implicated in Treg cell homeostasis. Recently, in a large animal model of hemorrhage, TGF-β levels were shown to be significantly increased 2 hours after injury, suggesting a possible mechanism for injury-related immune dysfunction.¹¹⁰ And although soluble CD154 was not increased following hemorrhage and traumatic brain injury in that study, in a murine model of mesenteric ischemia-reperfusion injury platelet expression of CD40 and CD154 was linked to remote organ damage.

Lymphocytes and T-Cell Immunity

The expression of genes associated with the adaptive immune response is rapidly altered following severe blunt trauma.² In fact, significant injury is associated with adaptive immune suppression that is characterized by altered cell-mediated immunity, specifically the balance between the major populations of Th cells. In fact, Th lymphocytes are functionally divided into subsets, which principally include Th1 and Th2 cells, as well as Th17 and inducible Treg cells. Derived from precursor CD4⁺ Th cells, each of these groups produces specific effector cytokines that are under unique transcriptional control. CD4 T cells play central roles in the function of the immune system through their effects on B-cell antibody production and their enhancement of specific Treg cell functions and macrophage activation. The specific functions of these cells include the recognition and killing of intracellular pathogens (cellular immunity; Th1 cells), regulation of antibody production (humoral immunity; Th2 cells), and maintenance of mucosal immunity and barrier integrity (Th17 cells). These activities have been characterized as proinflammatory (Th1) and anti-inflammatory (Th2), respectively, as determined by their distinct cytokine signatures (Fig. 2-11). Activation of Th1 cytokine-producing cells following injury has been linked to signaling events triggered by endogenous ligands, often composed of intracellular proteins (e.g., mitochondrial and nuclear-binding proteins) or ECM fragments released with cellular damage. As discussed earlier, these DAMPs are recognized by members of the TLR superfamily, including TLR2, TLR4, and TLR9, and can activate innate immune pathways.

A healthy immune response depends on a balanced Th1/Th2 response. Following injury, however, there is a reduction in Th1 cell differentiation and cytokine production in favor of an increased population of Th2 lymphocytes and their signaling products. As a consequence, both macrophage activation and proinflammatory cytokine synthesis are inhibited. This imbalance,

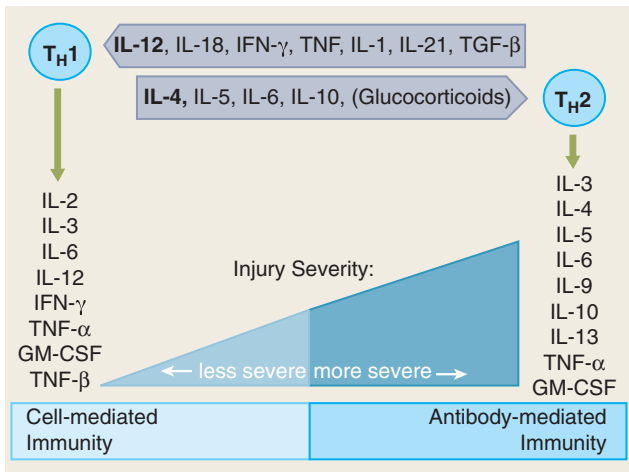


Figure 2-11. Specific immunity mediated by helper T lymphocytes subtype 1 (T_H1) and subtype 2 (T_H2) after injury. A T_H1 response is favored in lesser injuries, with intact cell-mediated and opsonizing antibody immunity against microbial infections. This cell-mediated immunity includes activation of monocytes, B lymphocytes, and cytotoxic T lymphocytes. A shift toward the T_H2 response from naïve helper T cells is associated with injuries of greater magnitude and is not as effective against microbial infections. A T_H2 response includes the activation of eosinophils, mast cells, and B-lymphocyte immunoglobulin 4 and immunoglobulin E production. (Primary stimulants and principal cytokine products of such responses are in **bold** characters.) Interleukin-4 (IL-4) and IL-10 are known inhibitors of the T_H1 response. Interferon- γ (IFN- γ) is a known inhibitor of the T_H2 response. Although not cytokines, glucocorticoids are potent stimulants of a T_H2 response, which may partly contribute to the immunosuppressive effects of cortisol. GM-CSF = granulocyte-macrophage colony-stimulating factor; IL = interleukin; TGF = transforming growth factor; TNF = tumor necrosis factor. (Adapted with permission from Lin E, Calvano SE, Lowry SF. *Inflammatory cytokines and cell response in surgery*. Surgery. 2000;127:117. Copyright Elsevier.)

which may be associated with decreased IL-12 production by activated monocytes/macrophages, has been associated with increased risk of infectious complications following surgery and trauma. What are the systemic mechanisms responsible for this shift? Several events have been implicated, including the direct effect of glucocorticoids on monocyte IL-12 production and T-cell IL-12 receptor expression. In addition, sympathoadrenal catecholamine production has also been demonstrated to reduce IL-12 production and proinflammatory cytokine synthesis.¹¹¹ Finally, more recent work has implicated circulating immature myeloid cells, termed **myeloid-derived suppressor cells**, that have immune suppressive activity particularly through their increased expression of arginase.¹¹² These cells have the potential to deplete the microenvironment of arginine, leading to further T-cell dysfunction.

Recent evidence suggests that Th17 cells and their effector cytokines, IL-17, IL-21, and IL-22, regulate mucosal immunity and barrier function. While their specific role in the inflammatory response following trauma is not well understood, both murine and human studies indicate that normal Th17 effector functions are disordered following burn injury, due to the inhibition of normal Th17 cell development by IL-10.¹¹³ These changes may contribute to remote organ damage and further susceptibility to infection in this setting.

Dendritic Cells

Recent studies have focused on the cellular components of the immune system in the context of polytrauma. While the activation of granulocytes and monocyte/macrophages following trauma has been well described, more recent work has also demonstrated that **dendritic cells (DCs)** are also activated in response to damage signals, to stimulate both the innate and the adaptive immune responses. For example, primary “danger signals” that are recognized and activated by DCs include debris from damaged or dying cells (e.g., HMGB1, nucleic acids including single nucleotides, and degradation products of the ECM). DCs are specialized antigen-presenting cells (APCs) that have three major functions. They are frequently referred to as “professional APCs” since their principal function is to capture, process, and present both endogenous and exogenous antigens, which, along with their costimulatory molecules, are capable of inducing a primary immune response in resting naïve T lymphocytes. In addition, they have the capacity to further regulate the immune response, both positively and negatively, through the upregulation and release of immunomodulatory molecules such as the chemokine CCL5 and the CXC chemokine CXCL5. Finally, they have been implicated both in the induction and maintenance of immune tolerance as well as in the acquisition of immune memory.¹¹⁴ There are distinct classes and subsets of DC, which are functionally heterogeneous. Further, subsets of DC at distinct locations have been shown to express different levels damage-sensing receptors (e.g., TLR) that dictate a preferential response to DAMP at that site. While relatively small in number relative to the total leukocyte population, the diverse distribution of DC in virtually all body tissues underlines their potential for a collaborative role in the initiation of the trauma-induced sterile systemic inflammatory response.

Eosinophils

Eosinophils are immunocytes whose primary functions are antihelminthic. Eosinophils are found mostly in tissues such as the lung and gastrointestinal tract, which may suggest a role in immune surveillance. Eosinophils can be activated by IL-3, IL-5, GM-CSF, chemoattractants, and platelet-activating factor. Eosinophil activation can lead to subsequent release of toxic mediators, including ROSs, histamine, and peroxidase.¹¹⁵

Mast Cells

Mast cells are important in the primary response to injury because they are located in tissues. TNF release from mast cells has been found to be crucial for neutrophil recruitment and pathogen clearance. Mast cells are also known to play an important role in the anaphylactic response to allergens. On activation from stimuli including allergen binding, infection, and trauma, mast cells produce histamine, cytokines, eicosanoids, proteases, and chemokines, which leads to vasodilatation, capillary leakage, and immunocyte recruitment. Mast cells are thought to be important cosignaling effector cells of the immune system via the release of IL-3, IL-4, IL-5, IL-6, IL-10, IL-13, and IL-14, as well as macrophage migration-inhibiting factor.¹¹⁶

Monocyte/Macrophages

Monocytes are mononuclear phagocytes that circulate in the bloodstream and can differentiate into macrophages, osteoclasts, and DCs on migrating into tissues. Macrophages are the main effector cells of the immune response to infection and

injury, primarily through mechanisms that include phagocytosis of microbial pathogens, release of inflammatory mediators, and clearance of apoptotic cells. Moreover, these cells fulfill homeostatic roles beyond host defense by performing important functions in the remodeling of tissues, both during development and in the adult animal.

In tissues, mononuclear phagocytes are quiescent. However, they respond to external cues (e.g., PAMPs, DAMPs, activated lymphocytes) by changing their phenotype. In response to various signals, macrophages may undergo classical M1 activation (stimulated by TLR ligands and IFN- γ) or alternative M2 activation (stimulated by type II cytokines IL-4/IL-13); these states mirror the Th1-Th2 polarization of T cells. The M1 phenotype is characterized by the expression of high levels of proinflammatory cytokines, like TNF- α , IL-1, and IL-6, in addition to the synthesis of ROS and RNS. M1 macrophages promote a strong Th1 response. In contrast, M2 macrophages are considered to be involved in the promotion of wound repair and the restoration of immune homeostasis through their expression of arginase-1 and IL-10, in addition to a variety of PRRs (e.g., scavenging molecules).¹¹⁷

In humans, downregulation of monocyte TNFR expression has been demonstrated experimentally and clinically during systemic inflammation. In clinical sepsis, nonsurviving patients with severe sepsis have an immediate reduction in monocyte surface TNFR expression with failure to recover, whereas surviving patients have normal or near-normal receptor levels from the onset of clinically defined sepsis. In patients with congestive heart failure, there is also a significant decrease in the amount of monocyte surface TNFR expression compared with control patients. In experimental models, endotoxin has been shown to differentially regulate over 1000 genes in murine macrophages with approximately 25% of these corresponding to cytokines and chemokines. During sepsis, macrophages undergo phenotypic reprogramming highlighted by decreased surface human leukocyte antigen DR (a critical receptor in antigen presentation), which also may contribute to host immunocompromise during sepsis.¹¹⁸

Neutrophils

Neutrophils are among the first responders to sites of infection and injury and, as such, are potent mediators of acute inflammation. Chemotactic mediators from a site of injury induce neutrophil adherence to the vascular endothelium and promote eventual cell migration into the injured tissue. Neutrophils are circulating immunocytes with short half-lives (4 to 10 hours). However, inflammatory signals may promote the longevity of neutrophils in target tissues, which can contribute to their potential detrimental effects and bystander injury. Once primed and activated by inflammatory stimuli, including TNF, IL-1, and microbial pathogens, neutrophils are able to enlist a variety of killing mechanisms to manage invading pathogens. Phagocytosed bacteria are killed using NADPH oxygenase-dependent generation of ROS or by releasing lytic enzymes and antibacterial proteins into the phagosome. Neutrophils can also dump their granule contents into the extracellular space, and many of these proteins also have important effects on the innate and adaptive immune responses. When highly activated, neutrophils can also extrude a meshwork of chromatin fibers, composed of DNA and histones that are decorated with granule contents. Termed neutrophil extracellular traps (NETs), this is an effective mechanism whereby neutrophils can immobilize bacteria to

facilitate their killing.¹¹⁹ NETs may also serve to prime T cells, making their threshold for activation lower.

Neutrophils do facilitate the recruitment of monocytes into inflamed tissues. These recruited cells are capable of phagocytosing apoptotic neutrophils to contribute to resolution of the inflammatory response.¹²⁰

ENDOTHELIUM-MEDIATED INJURY

Vascular Endothelium

Under physiologic conditions, vascular endothelium has overall anticoagulant properties mediated via the production and cell surface expression of heparin sulfate, dermatan sulfate, tissue factor pathway inhibitor, protein S, thrombomodulin, plasminogen, and tissue plasminogen activator. Endothelial cells also perform a critical function as barriers that regulate tissue migration of circulating cells. During sepsis, endothelial cells are differentially modulated, which results in an overall procoagulant shift via decreased production of anticoagulant factors, which may lead to microthrombosis and organ injury.

Neutrophil-Endothelium Interaction

The regulated inflammatory response to infection facilitates neutrophil and other immunocyte migration to compromised regions through the actions of increased vascular permeability, chemoattractants, and increased endothelial adhesion factors referred to as *selectins* that are elaborated on cell surfaces (Table 2-7). In response to inflammatory stimuli released from sentinel leukocytes in the tissues, including chemokines, thrombin, leukotrienes, histamine, and TNF, vascular endothelium are activated and their surface protein expression is altered. Within 10 to 20 minutes, prestored reservoirs of the adhesion molecule P-selectin are mobilized to the cell surface where it can mediate neutrophil recruitment (Fig. 2-12). After 2 hours, endothelial cell transcriptional processes provide additional surface expression of E-selectin. E-selectin and P-selectin bind P-selectin glycoprotein ligand-1 (PSGL-1) on the neutrophils to orchestrate the capture and rolling of these leukocytes and allow targeted immunocyte extravasation. Immobilized chemokines on the endothelial surface create a chemotactic gradient to further enhance immune cell recruitment.¹²¹ Also important are secondary leukocyte-leukocyte interactions in which PSGL-1 and L-selectin binding facilitates further leukocyte tethering. Although there are distinguishable properties among individual selectins in leukocyte rolling, effective rolling most likely involves a significant degree of functional overlap.¹²²

Chemokines

Chemokines are a family of small proteins (8 to 13 kDa) that were first identified through their chemotactic and activating effects on inflammatory cells. They are produced at high levels following nearly all forms of injury in all tissues, where they are key attractants for immune cell extravasation. There are more than 50 different chemokines and 20 chemokine receptors that have been identified. Chemokines are released from endothelial cells, mast cells, platelets, macrophages, and lymphocytes. They are soluble proteins, which when secreted, bind to glycosaminoglycans on the cell surface or in the ECM. In this way, the chemokines can form a fixed chemical gradient that promotes immune cell exit to target areas. Chemokines are distinguished (in general) from cytokines by virtue of their receptors, which are members of the G-protein-coupled receptor superfamily.

Table 2-7

Molecules that mediate leukocyte-endothelial adhesion, categorized by family

ADHESION MOLECULE	ACTION	ORIGIN	INDUCERS OF EXPRESSION	TARGET CELLS
<i>Selectins</i>				
L-selectin	Fast rolling	Leukocytes	Native	Endothelium, platelets, eosinophils
P-selectin	Slow rolling	Platelets and endothelium	Thrombin, histamine	Neutrophils, monocytes
E-selectin	Very slow rolling	Endothelium	Cytokines	Neutrophils, monocytes, lymphocytes
<i>Immunoglobulins</i>				
ICAM-1	Firm adhesion/transmigration	Endothelium, leukocytes, fibroblasts, epithelium	Cytokines	Leukocytes
ICAM-2	Firm adhesion	Endothelium, platelets	Native	Leukocytes
VCAM-1	Firm adhesion/transmigration	Endothelium	Cytokines	Monocytes, lymphocytes
PECAM-1	Adhesion/transmigration	Endothelium, platelets, leukocytes	Native	Endothelium, platelets, leukocytes
β_2 -(CD18) Integrins				
CD18/11a	Firm adhesion/transmigration	Leukocytes	Leukocyte activation	Endothelium
CD18/11b (Mac-1)	Firm adhesion/transmigration	Neutrophils, monocytes, natural killer cells	Leukocyte activation	Endothelium
CD18/11c	Adhesion	Neutrophils, monocytes, natural killer cells	Leukocyte activation	Endothelium
β_1 -(CD29) Integrins				
VLA-4	Firm adhesion/transmigration	Lymphocytes, monocytes	Leukocyte activation	Monocytes, endothelium, epithelium

ICAM-1 = intercellular adhesion molecule-1; ICAM-2 = intercellular adhesion molecule-2; Mac-1 = macrophage antigen 1; PECAM-1 = platelet-endothelial cell adhesion molecule-1; VCAM-1 = vascular cell adhesion molecule-1; VLA-4 = very late antigen-4.

Most chemokine receptors recognize more than one chemokine ligand, leading to redundancy in chemokine signaling.

The chemokines are subdivided into families based on their amino acid sequences at their N-terminus. For example, *CC chemokines* contain two N-terminus **cysteine** residues that are immediately adjacent (hence the “C-C” designation), whereas the N-terminal cysteines in *CXC chemokines* are separated by a single amino acid. The CXC chemokines are particularly important for neutrophil (PMN) proinflammatory function. Members of the CXC chemokine family, which include IL-8, induce neutrophil migration and secretion of cytotoxic granular contents and metabolites. Additional chemokine families include the C and CX3C chemokines.¹²¹

Nitric Oxide

Nitric oxide (NO) was initially known as *endothelium-derived relaxing factor* due to its effect on vascular smooth muscle. Normal vascular smooth muscle cell relaxation is maintained by a constant output of NO that is regulated in the endothelium by both flow- and receptor-mediated events. NO can also reduce microthrombosis by reducing platelet adhesion and aggregation (Fig. 2-13) and interfering with leukocyte adhesion to the endothelium. NO easily traverses cell membranes, has a short half-life of a few seconds, and is oxidized into nitrate and nitrite.

Endogenous NO formation is derived largely from the action of NO synthase (NOS), which is constitutively expressed in endothelial cells (NOS3). NOS generates NO by catalyzing the degradation of L-arginine to L-citrulline and NO, in the presence of oxygen and NADPH. There are two additional isoforms of NOS: neuronal NOS (NOS1) and inducible NOS (iNOS/NOS2). The vasodilatory effects of NO are mediated by **guanylyl cyclase**, an enzyme that is found in vascular smooth muscle cells and most other cells of the body. When NO is formed by endothelium, it rapidly diffuses into adjacent cells where it binds to and activates guanylyl cyclase. This enzyme catalyzes the dephosphorylation of guanosine triphosphate (GTP) to cyclic guanosine monophosphate (**cGMP**), which serves as a second messenger for many important cellular functions, particularly for signaling smooth muscle relaxation.

NO synthesis is increased in response to proinflammatory mediators such as TNF- α and IL-1 β , as well as microbial products, due to the upregulation of iNOS expression.¹²³ In fact, studies in both animal models and humans have shown that severe systemic injury and associated hemorrhage produce an early upregulation of iNOS in the liver, lung, spleen, and vascular system. In these circumstances, NO is reported to function as an immunoregulator, which is capable of modulating cytokine production and immune cell development. In particular, recent data support a role for iNOS in the regulation of T-cell

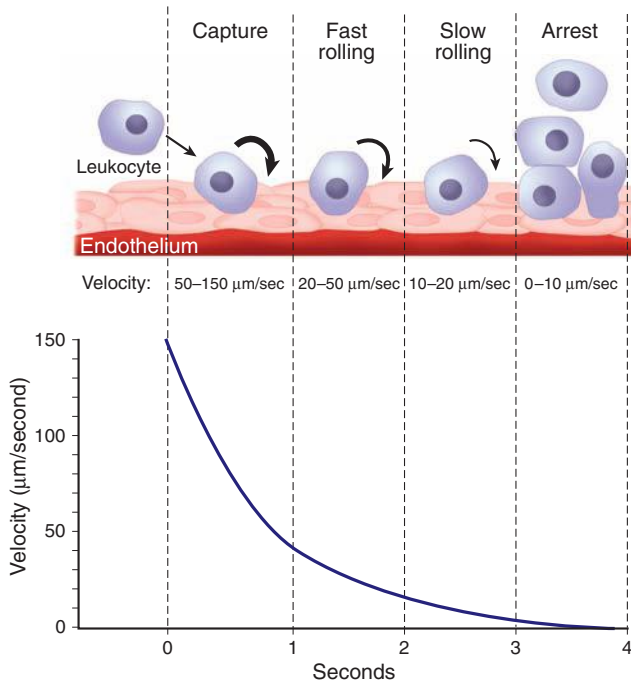


Figure 2-12. Simplified sequence of selectin-mediated neutrophil-endothelium interaction after an inflammatory stimulus. **CAPTURE** (tethering), predominantly mediated by cell L-selectin with contribution from endothelial P-selectin, describes the initial recognition between leukocyte and endothelium, in which circulating leukocytes marginate toward the endothelial surface. **FAST ROLLING** (20 to 50 $\mu\text{m/s}$) is a consequence of rapid L-selectin shedding from cell surfaces and formation of new downstream L-selectin to endothelium bonds, which occur in tandem. **SLOW ROLLING** (10 to 20 $\mu\text{m/s}$) is predominantly mediated by P-selectins. The slowest rolling (3 to 10 $\mu\text{m/s}$) before arrest is predominantly mediated by E-selectins, with contribution from P-selectins. **ARREST** (firm adhesion) leading to transmigration is mediated by β -integrins and the immunoglobulin family of adhesion molecules. In addition to interacting with the endothelium, activated leukocytes also recruit other leukocytes to the inflammatory site by direct interactions, which are mediated in part by selectins. (Adapted with permission from Lin E, Calvano SE, Lowry SF. Selectin neutralization: does it make biological sense? Crit Care Med. 1999;27:2050.)

dysfunction in the setting of trauma as evidenced by suppressed proliferative and Th1 cytokine release.¹²⁴

Increased NO is also detectable in septic shock, where it is associated with low peripheral vascular resistance and hypotension. Increased production of NO in this setting correlates with changes in vascular permeability and inhibition of noradrenergic nerve transmission. While the increased NO in sepsis is largely attributed to greater iNOS activity and expression, cytokines are reported to modulate NO release by increasing arginine availability through the expression of the cationic amino acid transporter (CAT) or by increasing tetrahydrobiopterin levels, a key cofactor in NO synthesis. Additional effects associated with excess NO include protein and membrane phospholipid alterations by nitrosylation and the inhibition of mitochondrial respiration. Inhibition of NO production seemed initially to be a promising strategy in patients with severe sepsis. However, a randomized clinical trial in patients with septic shock determined that treatment with a *nonselective* NOS inhibitor was

associated with an increase in mortality compared with placebo.¹²⁵ More recent data using an ovine model of peritonitis demonstrated that selective iNOS inhibition reduced pulmonary artery hypertension and gas exchange impairment and promoted higher visceral organ blood flow, coinciding with lower plasma cytokine concentrations.¹²⁶ These data suggest that specific targeting of iNOS in the setting of sepsis may remain a viable therapeutic option.

Prostacyclin

The immune effects of prostacyclin (PGI_2) were discussed earlier. The best described effects of PGI_2 are in the cardiovascular system, however, where it is produced by vascular endothelial cells. Prostacyclin is a potent vasodilator that also inhibits platelet aggregation. In the pulmonary system, PGI_2 reduces pulmonary blood pressure and bronchial hyperresponsiveness. In the kidneys, PGI_2 modulates renal blood flow and glomerular filtration rate. Prostacyclin acts through its receptor (a G-protein-coupled receptor of the rhodopsin family) to stimulate the enzyme adenylate cyclase, allowing the synthesis of cAMP from adenosine triphosphate (ATP). This leads to a cAMP-mediated decrease in intracellular calcium and subsequent smooth muscle relaxation.

During systemic inflammation, endothelial prostacyclin expression is impaired, and thus the endothelium favors a more procoagulant profile. Exogenous prostacyclin analogues, both intravenous and inhaled, have been used to improve oxygenation in patients with acute lung injury. Early clinical studies with prostacyclin have delivered some encouraging results, showing that infusion of prostacyclin improved cardiac index, splanchnic blood flow as measured by intestinal tonometry, and oxygen delivery in patients with sepsis. Importantly, there was no significant decrease in mean arterial pressure.¹²⁷

Endothelins

Endothelins (ETs) are potent mediators of vasoconstriction and are composed of three members: ET-1, ET-2, and ET-3. ETs are 21-amino-acid peptides derived from a 38-amino-acid precursor molecule. ET-1, synthesized primarily by endothelial cells, is the most potent endogenous vasoconstrictor and is estimated to be 10 times more potent than angiotensin II. ET release is upregulated in response to hypotension, LPS, injury, thrombin, TGF- β , IL-1, angiotensin II, vasopressin, catecholamines, and anoxia. ETs are primarily released to the abluminal side of endothelial cells, and very little is stored in cells; thus a plasma increase in ET is associated with a marked increase in production. The half-life of plasma ET is between 4 and 7 minutes, which suggests that ET release is primarily regulated at the transcriptional level. Three ET receptors, referred to as ET_A , ET_B , and ET_C , have been identified and function via the G-protein-coupled receptor mechanism. ET_B receptors are associated with increased NO and prostacyclin production, which may serve as a feedback mechanism. Atrial ET_A receptor activation has been associated with increased inotropy and chronotropy. ET-1 infusion is associated with increased pulmonary vascular resistance and pulmonary edema and may contribute to pulmonary abnormalities during sepsis. At low levels, in conjunction with NO, ETs regulate vascular tone. However, at increased concentrations, ETs can disrupt the normal blood flow and distribution and may compromise oxygen delivery to the tissue. Recent data link ET expression in pulmonary vasculature with persistent inflammation associated with the development of

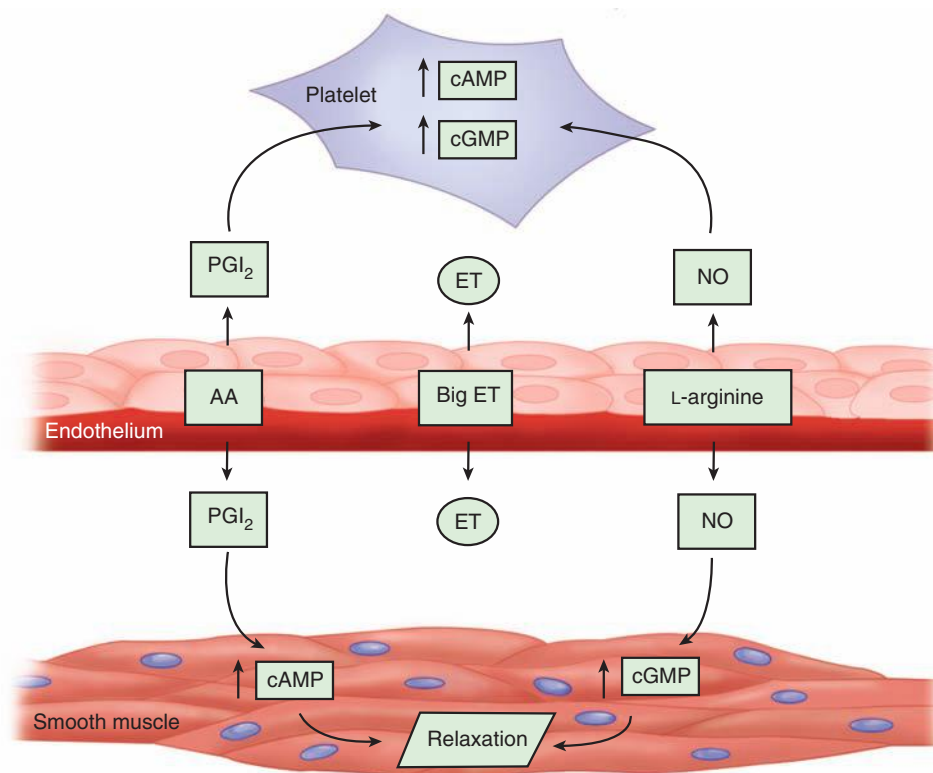


Figure 2-13. Endothelial interaction with smooth muscle cells and with intraluminal platelets. Prostacyclin (prostaglandin I₂, or PGI₂) is derived from arachidonic acid (AA), and nitric oxide (NO) is derived from L-arginine. The increase in cyclic adenosine monophosphate (cAMP) and cyclic guanosine monophosphate (cGMP) results in smooth muscle relaxation and inhibition of platelet thrombus formation. Endothelins (ETs) are derived from “big ET,” and they counter the effects of prostacyclin and NO.

pulmonary hypertension.¹²⁸ ET expression is linked to posttranslational and transcriptional initiation of the unfolded protein response in the affected cells, which results in the production of inflammatory cytokines. Finally, ET-1 levels correlate with levels of brain natriuretic peptide and CRP, as well as the Sequential Organ Failure Assessment score in septic patients.¹²⁹

Platelet-Activating Factor

Phosphatidylcholine is a major lipid constituent of the plasma membrane. Its enzymatic processing by cytosolic phospholipase A₂ (cPLA₂) or calcium-independent phospholipase A₂ (iPLA₂) generates powerful small lipid molecules, which function as intracellular second messengers. One of these is arachidonic acid, the precursor molecule for eicosanoids. Another is **platelet-activating factor** (PAF). During acute inflammation, PAF is released by immune cells following the activation of PLA₂. The receptor for PAF (PAFR), which is constitutively expressed by platelets, leukocytes, and endothelial cells, is a G-protein-coupled receptor of the rhodopsin family. Ligand binding to the PAFR promotes the activation and aggregation of platelets and leukocytes, leukocyte adherence, motility, chemotaxis, and invasion, as well as ROS generation.¹³⁰ Additionally, PAF activation of human PMNs induces extrusion of NETs, while platelet activation induces IL-1 via a novel posttranscriptional mechanism. Finally, PAFR ligation results not only in the upregulation of numerous proinflammatory genes including COX-2, iNOS, and IL-6, but also in the generation of lipid intermediates such as arachidonic acid and lysophospholipids through the activation of PLA₂. Antagonists to PAF receptors have been experimentally shown to mitigate the effects of ischemia and reperfusion injury. Of note, human sepsis is associated with a reduction in the levels of PAF-acetylhydrolase, which inactivates PAF by removing an acetyl group. Indeed,

PAF-acetylhydrolase administration in patients with severe sepsis has yielded some reduction in multiple organ dysfunction and mortality¹³¹; however, larger phase III clinical trials failed to show benefit.

Natriuretic Peptides

The natriuretic peptides, atrial natriuretic factor (ANF) and brain natriuretic peptide (BNP), are a family of peptides that are released primarily by atrial tissue but are also synthesized by the gut, kidney, brain, adrenal glands, and endothelium. The functionally active forms of the peptides are C-terminal fragments of a larger prohormone, and both N- and C-terminal fragments are detectable in the blood (referred to a N-terminal pro-BNP and pro-ANF, respectively). ANF and BNP share most biologic properties including diuretic, natriuretic, vasorelaxant, and cardiac remodeling properties that are effected by signaling through a common receptor: the guanylyl cyclase-A (GC-A) receptor. They are both increased in the setting of cardiac disorders; however, recent evidence indicates some distinctions in the setting of inflammation. For example, endotoxemia in healthy volunteers increased plasma N-terminal pro-BNP without changing heart rate and blood pressure. Also, elevated pro-BNP has been detected in septic patients in the absence of myocardial dysfunction and appears to have prognostic significance.¹³²

SURGICAL METABOLISM

The initial hours after surgical or traumatic injury are metabolically associated with a reduced total body energy expenditure and urinary nitrogen wasting. On adequate resuscitation and stabilization of the injured patient, a reprioritization of substrate use ensues to preserve vital organ function and to support repair of injured tissue. This phase of recovery also is characterized

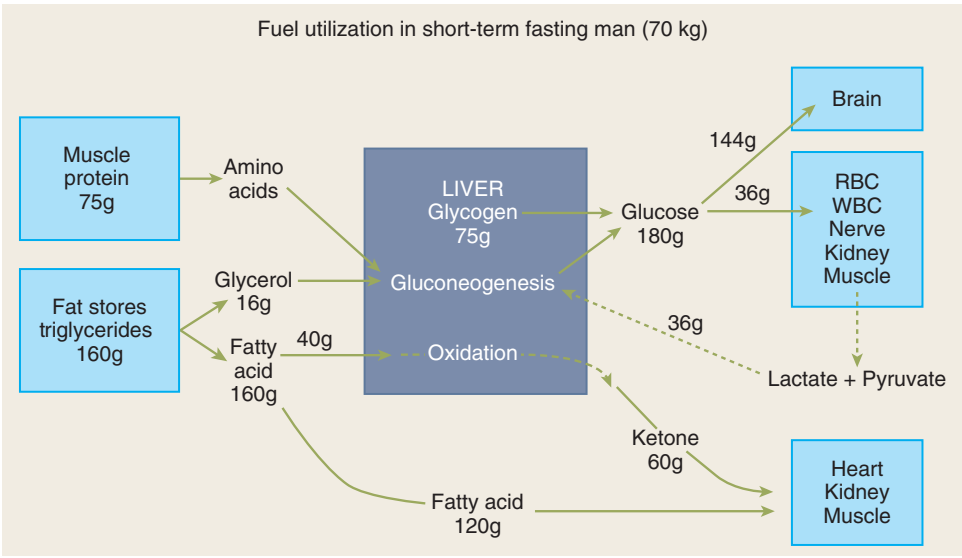


Figure 2-14. Fuel utilization in a 70-kg man during short-term fasting with an approximate basal energy expenditure of 1800 kcal. During starvation, muscle proteins and fat stores provide fuel for the host, with the latter being most abundant. RBC = red blood cell; WBC = white blood cell. (Adapted from Cahill GF: *Starvation in man*. N Engl J Med. 1970;282:668.)

by functions that participate in the restoration of homeostasis, such as augmented metabolic rates and oxygen consumption, enzymatic preference for readily oxidizable substrates such as glucose, and stimulation of the immune system. Understanding of the collective alterations in amino acid (protein), carbohydrate, and lipid metabolism characteristic of the surgical patient lays the foundation upon which metabolic and nutritional support can be implemented.

Metabolism during Fasting

Fuel metabolism during unstressed fasting states has historically served as the standard to which metabolic alterations after acute injury and critical illness are compared (Fig. 2-14). To maintain basal metabolic needs (i.e., at rest and fasting), a normal healthy adult requires approximately 22 to 25 kcal/kg per day drawn from carbohydrate, lipid, and protein sources. This requirement can be as high as 40 kcal/kg per day in severe stress states, such as those seen in patients with burn injuries.

In the healthy adult, principal sources of fuel during short-term fasting (<5 days) are derived from muscle protein and body fat, with fat being the most abundant source of energy (Table 2-8). The normal adult body contains 300 to 400 g of carbohydrates in the form of glycogen, of which 75 to 100 g are stored in the liver. Approximately 200 to 250 g of glycogen are stored within skeletal, cardiac, and smooth muscle cells. The greater glycogen stores within the muscle are not readily available for systemic use due to a deficiency in glucose-6-phosphatase but are available for the energy needs of muscle cells. Therefore, in the fasting state, hepatic glycogen stores are rapidly and preferentially depleted, which results in a fall of serum glucose concentration within hours (<16 hours).

During fasting, a healthy 70-kg adult will use 180 g of glucose per day to support the metabolism of obligate glycolytic cells such as neurons, leukocytes, erythrocytes, and the renal medullae. Other tissues that use glucose for fuel are skeletal muscle, intestinal mucosa, fetal tissues, and solid tumors.

Table 2-8

**A. Body fuel reserves in a 70-kg man and
B. Energy equivalent of substrate oxidation**

A. COMPONENT			MASS (kg)	ENERGY (kcal)	DAYS AVAILABLE
Water and minerals			49	0	0
Protein			6.0	24,000	13.0
Glycogen			0.2	800	0.4
Fat			15.0	140,000	78.0
Total			70.2	164,800	91.4
B. SUBSTRATE	O ₂ CONSUMED (L/g)	CO ₂ PRODUCED (L/g)	RESPIRATORY QUOTIENT	kcal/g	RECOMMENDED DAILY REQUIREMENT
Glucose	0.75	0.75	1.0	4.0	7.2 g/kg per day
Dextrose	—	—	—	3.4	—
Lipid	2.0	1.4	0.7	9.0	1.0 g/kg per day
Protein	1.0	0.8	0.8	4.0	0.8 g/kg per day

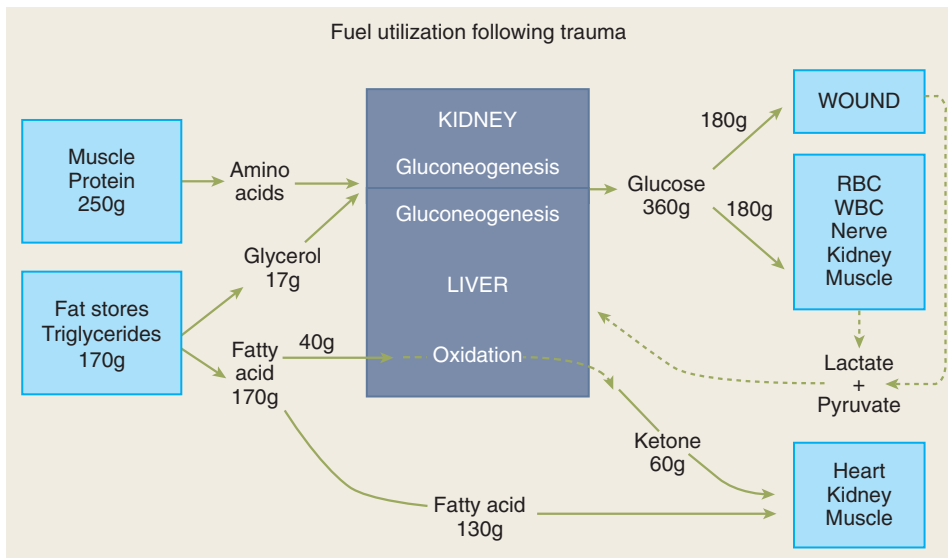


Figure 2-17. Acute injury is associated with significant alterations in substrate utilization. There is enhanced nitrogen loss, indicative of catabolism. Fat remains the primary fuel source under these circumstances. RBC = red blood cell; WBC = white blood cell.

ammonium ions. The kidneys also participate in gluconeogenesis by the use of glutamine and glutamate, and can become the primary source of gluconeogenesis during prolonged starvation, accounting for up to one half of systemic glucose production.

Lipid stores within adipose tissue provide 40% or more of caloric expenditure during starvation. Energy requirements for basal enzymatic and muscular functions (e.g., gluconeogenesis, neural transmission, and cardiac contraction) are met by the mobilization of triglycerides from adipose tissue. In a resting, fasting, 70-kg person, approximately 160 g of free fatty acids and glycerol can be mobilized from adipose tissue per day. Free fatty acid release is stimulated in part by a reduction in serum insulin levels and in part by the increase in circulating glucagon and catecholamine. Such free fatty acids, like ketone bodies, are used as fuel by tissues such as the heart, kidney (renal cortex), muscle, and liver. The mobilization of lipid stores for energy importantly decreases the rate of glycolysis, gluconeogenesis, and proteolysis, as well as the overall glucose requirement to sustain the host. Furthermore, ketone bodies spare glucose utilization by inhibiting the enzyme pyruvate dehydrogenase.

Metabolism after Injury

Injuries or infections induce unique neuroendocrine and immunologic responses that differentiate injury metabolism from that of unstressed fasting (Fig. 2-17). The magnitude of metabolic expenditure appears to be directly proportional to the severity of insult, with thermal injuries and severe infections having the highest energy demands (Fig. 2-18). The increase in energy expenditure is mediated in part by sympathetic activation and catecholamine release, which has been replicated by the administration of catecholamines to healthy human subjects. Lipid metabolism after injury is intentionally discussed first, because this macronutrient becomes the primary source of energy during stressed states.¹³⁴

Lipid Metabolism after Injury

Lipids are not merely nonprotein, noncarbohydrate fuel sources that minimize protein catabolism in the injured patient. Lipid metabolism potentially influences the structural integrity of cell membranes as well as the immune response during systemic inflammation. Adipose stores within the body (triglycerides) are

the predominant energy source (50% to 80%) during critical illness and after injury. Fat mobilization (lipolysis) occurs mainly in response to catecholamine stimulus of the hormone-sensitive triglyceride lipase. Other hormonal influences that potentiate lipolysis include adrenocorticotropic hormone (ACTH), catecholamines, thyroid hormone, cortisol, glucagon, GH release, and reduction in insulin levels.¹³⁵

Lipid Absorption. Although the process is poorly understood, adipose tissue provides fuel for the host in the form of free fatty acids and glycerol during critical illness and injury. Oxidation of 1 g of fat yields approximately 9 kcal of energy. Although the liver is capable of synthesizing triglycerides from carbohydrates and

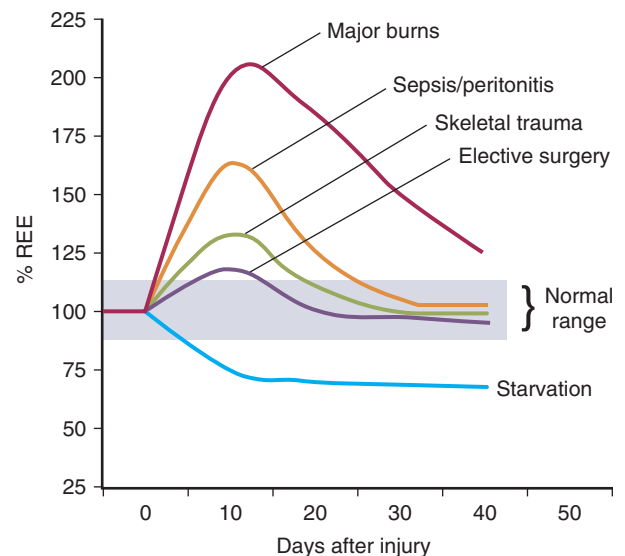


Figure 2-18. Influence of injury severity on resting metabolism (resting energy expenditure, or REE). The shaded area indicates normal REE. (From Long CL, Schaffel N, Geiger J, et al. *Metabolic response to injury and illness: estimation of energy and protein needs from indirect calorimetry and nitrogen balance*. JPEN J Parenter Enteral Nutr. 1979;3(6):452. Copyright © 1979 by A.S.P.E.N. Reprinted by permission of Sage Publications.)

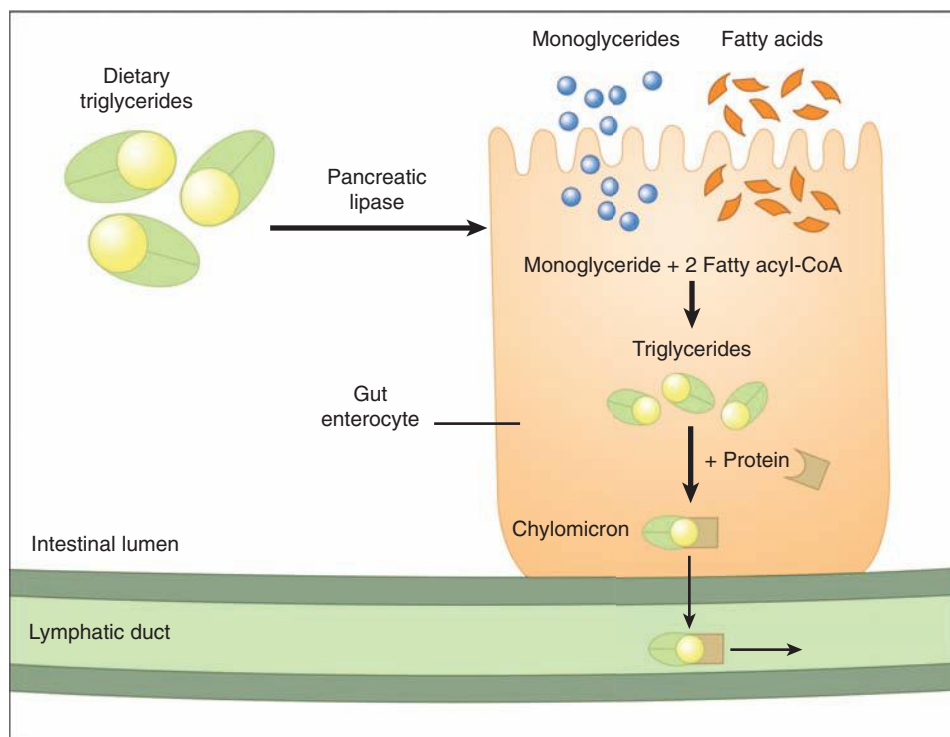


Figure 2-19. Pancreatic lipase within the small intestinal brush borders hydrolyzes triglycerides into monoglycerides and fatty acids. These components readily diffuse into the gut enterocytes, where they are re-esterified into triglycerides. The resynthesized triglycerides bind carrier proteins to form chylomicrons, which are transported by the lymphatic system. Shorter triglycerides (those with <10 carbon atoms) can bypass this process and directly enter the portal circulation for transport to the liver. CoA = coenzyme A.

amino acids, dietary and exogenous sources provide the major source of triglycerides. Dietary lipids are not readily absorbable in the gut but require pancreatic lipase and phospholipase within the duodenum to hydrolyze the triglycerides into free fatty acids and monoglycerides. The free fatty acids and monoglycerides are then readily absorbed by gut enterocytes, which resynthesize triglycerides by esterification of the monoglycerides with fatty acyl coenzyme A (acyl-CoA) (Fig. 2-19). Long-chain triglycerides (LCTs), defined as those with 12 carbons or more, generally undergo this process of esterification and enter the circulation through the lymphatic system as chylomicrons. Shorter fatty acid chains directly enter the portal circulation and are transported to the liver by albumin carriers. Hepatocytes use free fatty acids as a fuel source during stress states but also can synthesize phospholipids or triglycerides (i.e., very-low-density lipoproteins) during fed states. Systemic tissue (e.g., muscle and the heart) can use chylomicrons and triglycerides as fuel by hydrolysis with lipoprotein lipase at the luminal surface of capillary endothelium.¹³⁶ Trauma or sepsis suppresses lipoprotein lipase activity in both adipose tissue and muscle, presumably mediated by TNF.

Lipolysis and Fatty Acid Oxidation. Periods of energy demand are accompanied by free fatty acid mobilization from adipose stores. This is mediated by hormonal influences (e.g., catecholamines, ACTH, thyroid hormones, GH, and glucagon) on triglyceride lipase through a cAMP pathway (Fig. 2-20). In adipose tissues, triglyceride lipase hydrolyzes triglycerides into free fatty acids and glycerol. Free fatty acids enter the capillary circulation and are transported by albumin to tissues requiring this fuel source (e.g., heart and skeletal muscle). Insulin inhibits lipolysis and favors triglyceride synthesis by augmenting lipoprotein lipase activity as well as intracellular levels of glycerol-3-phosphate. The use of glycerol for fuel depends on the availability of tissue glycerokinase, which is abundant in the liver and kidneys.

Free fatty acids absorbed by cells conjugate with acyl-CoA within the cytoplasm. The transport of fatty acyl-CoA from the outer mitochondrial membrane across the inner mitochondrial membrane occurs via the carnitine shuttle (Fig. 2-21). Medium-chain triglycerides (MCTs), defined as those 6 to 12 carbons in length, bypass the carnitine shuttle and readily cross the mitochondrial membranes. This accounts in part for the fact that MCTs are more efficiently oxidized than LCTs. Ideally, the rapid oxidation of MCTs makes them less prone to fat deposition, particularly within immune cells and the reticuloendothelial system—a common finding with lipid infusion in parenteral nutrition.¹³⁷ However, exclusive use of MCTs as fuel in animal studies has been associated with higher metabolic demands and toxicity, as well as essential fatty acid deficiency.

Within the mitochondria, fatty acyl-CoA undergoes beta oxidation, which produces acetyl-CoA with each pass through the cycle. Each acetyl-CoA molecule subsequently enters the tricarboxylic acid (TCA) cycle for further oxidation to yield 12 ATP molecules, carbon dioxide, and water. Excess acetyl-CoA molecules serve as precursors for ketogenesis. Unlike glucose metabolism, oxidation of fatty acids requires proportionally less oxygen and produces less carbon dioxide. This is frequently quantified as the ratio of carbon dioxide produced to oxygen consumed for the reaction and is known as the *respiratory quotient (RQ)*. An RQ of 0.7 would imply greater fatty acid oxidation for fuel, whereas an RQ of 1 indicates greater carbohydrate oxidation (overfeeding). An RQ of 0.85 suggests the oxidation of equal amounts of fatty acids and glucose.

Ketogenesis

Carbohydrate depletion slows the entry of acetyl-CoA into the TCA cycle secondary to depleted TCA intermediates and enzyme activity. Increased lipolysis and reduced systemic carbohydrate availability during starvation diverts excess acetyl-CoA toward hepatic ketogenesis. A number of extrahepatic

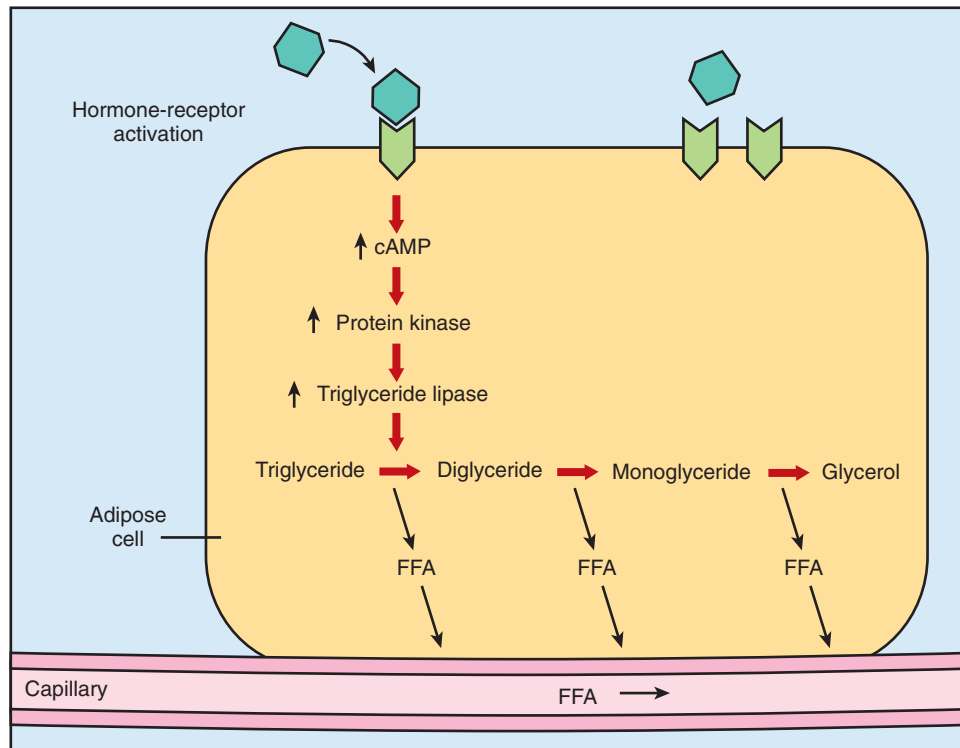


Figure 2-20. Fat mobilization in adipose tissue. Triglyceride lipase activation by hormonal stimulation of adipose cells occurs through the cyclic adenosine monophosphate (cAMP) pathway. Triglycerides are serially hydrolyzed with resultant free fatty acid (FFA) release at every step. The FFAs diffuse readily into the capillary bed for transport. Tissues with glycerokinase can use glycerol for fuel by forming glycerol-3-phosphate. Glycerol-3-phosphate can esterify with FFAs to form triglycerides or can be used as a precursor for renal and hepatic gluconeogenesis. Skeletal muscle and adipose cells have little glycerokinase and thus do not use glycerol for fuel.

tissues, but not the liver itself, are capable of using ketones for fuel. Ketosis represents a state in which hepatic ketone production exceeds extrahepatic ketone utilization.

The rate of ketogenesis appears to be inversely related to the severity of injury. Major trauma, severe shock, and sepsis attenuate ketogenesis by increasing insulin levels and by causing rapid tissue oxidation of free fatty acids. Minor injuries and infections are associated with modest elevations in plasma free fatty acid concentrations and ketogenesis. However, in minor stress states ketogenesis does not exceed that in nonstressed starvation.

Carbohydrate Metabolism

Ingested and enteral carbohydrates are primarily digested in the small intestine, where pancreatic and intestinal enzymes reduce the complex carbohydrates to dimeric units. Disaccharidases (e.g., sucrase, lactase, and maltase) within intestinal brush borders dismantle the complex carbohydrates into simple hexose units, which are transported into the intestinal mucosa. Glucose and galactose are primarily absorbed by energy-dependent active transport coupled to the sodium pump. Fructose absorption, however, occurs by concentration-dependent facilitated diffusion. Neither fructose or galactose within the circulation nor exogenous mannitol (for neurologic injury) evokes an insulin response. Intravenous administration of low-dose fructose in fasting humans has been associated with nitrogen conservation, but the clinical utility of fructose administration in human injury remains to be demonstrated.

Discussion of carbohydrate metabolism primarily refers to the utilization of glucose. The oxidation of 1 g of carbohydrate

yields 4 kcal, but sugar solutions such as those found in intravenous fluids or parenteral nutrition provide only 3.4 kcal/g of dextrose. In starvation, glucose production occurs at the expense of protein stores (i.e., skeletal muscle). Hence, the primary goal for maintenance glucose administration in surgical patients is to minimize muscle wasting. The exogenous administration of small amounts of glucose (approximately 50 g/d) facilitates fat entry into the TCA cycle and reduces ketosis. Unlike in starvation in healthy subjects, in septic and trauma patients, provision of exogenous glucose never has been shown to fully suppress amino acid degradation for gluconeogenesis. This suggests that during periods of stress, other hormonal and proinflammatory mediators have a profound influence on the rate of protein degradation and that some degree of muscle wasting is inevitable. The administration of insulin, however, has been shown to reverse protein catabolism during severe stress by stimulating protein synthesis in skeletal muscles and by inhibiting hepatocyte protein degradation. Insulin also stimulates the incorporation of elemental precursors into nucleic acids in association with RNA synthesis in muscle cells.

In cells, glucose is phosphorylated to form glucose-6-phosphate. Glucose-6-phosphate can be polymerized during glycogenesis or catabolized in glycogenolysis. Glucose catabolism occurs by cleavage to pyruvate or lactate (pyruvic acid pathway) or by decarboxylation to pentoses (pentose shunt) (Fig. 2-22).

Excess glucose from overfeeding, as reflected by RQs >1.0 , can result in conditions such as glucosuria, thermogenesis, and conversion to fat (lipogenesis). Excessive glucose administration results in elevated carbon dioxide production, which may

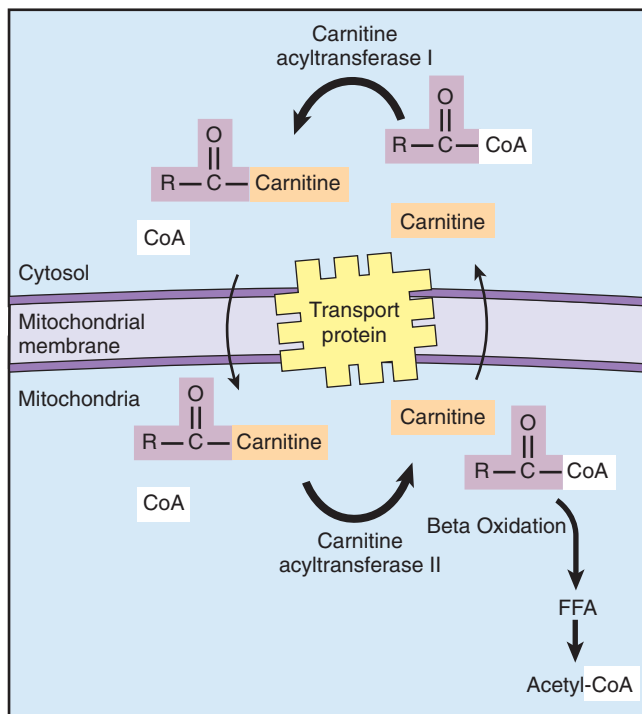


Figure 2-21. Free fatty acids (FFAs) in the cells form fatty acyl-coenzyme A (CoA) with CoA. Fatty acyl-CoA cannot enter the inner mitochondrial membrane and requires carnitine as a carrier protein (carnitine shuttle). Once inside the mitochondria, carnitine dissociates and fatty acyl-CoA is re-formed. The carnitine molecule is transported back into the cytosol for reuse. The fatty acyl-CoA undergoes beta oxidation to form acetyl-CoA for entry into the tricarboxylic acid cycle. “R” represents a part of the acyl group of acyl-CoA.

be deleterious in patients with suboptimal pulmonary function, as well as hyperglycemia, which may contribute to infectious risk and immune suppression.

Injury and severe infections acutely induce a state of peripheral glucose intolerance, despite ample insulin production at levels several fold above baseline. This may occur in part due to reduced skeletal muscle pyruvate dehydrogenase activity after injury, which diminishes the conversion of pyruvate to acetyl-CoA and subsequent entry into the TCA cycle. The three-carbon structures (e.g., pyruvate and lactate) that consequently accumulate are shunted to the liver as substrate for gluconeogenesis. Furthermore, regional tissue catheterization and isotope dilution studies have shown an increase in net splanchnic glucose production by 50% to 60% in septic patients and a 50% to 100% increase in burn patients.¹³⁷ The increase in plasma glucose levels is proportional to the severity of injury, and this net hepatic gluconeogenic response is believed to be under the influence of glucagon. Unlike in the nonstressed subject, in the hypermetabolic, critically ill patient, the hepatic gluconeogenic response to injury or sepsis cannot be suppressed by exogenous or excess glucose administration but rather persists. Hepatic gluconeogenesis, arising primarily from alanine and glutamine catabolism, provides a ready fuel source for tissues such as those of the nervous system, wounds, and erythrocytes, which do not require insulin for glucose transport. The elevated glucose concentrations also provide a necessary energy source for leukocytes in inflamed tissues and in sites of microbial invasions.

The shunting of glucose away from nonessential organs such as skeletal muscle and adipose tissues is mediated by catecholamines. Experiments with infusing catecholamines and glucagon in animals have demonstrated elevated plasma glucose levels as a result of increased hepatic gluconeogenesis and

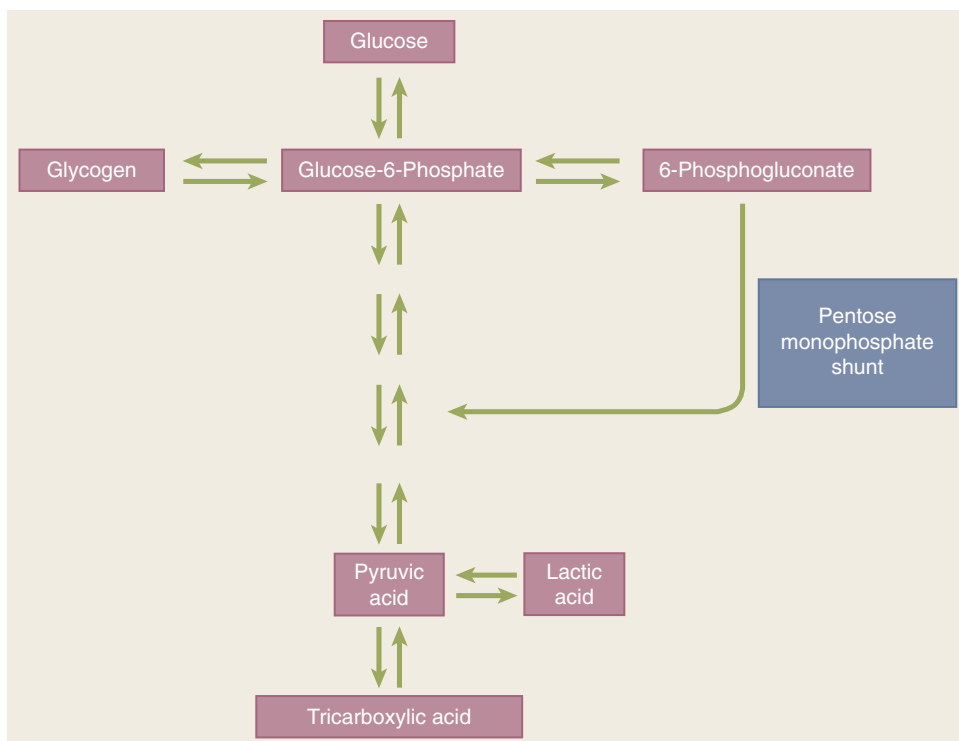


Figure 2-22. Simplified schema of glucose catabolism through the pentose monophosphate pathway or by breakdown into pyruvate. Glucose-6-phosphate becomes an important “crossroad” for glucose metabolism.

peripheral insulin resistance. Interestingly, although glucocorticoid infusion alone does not increase glucose levels, it does prolong and augment the hyperglycemic effects of catecholamines and glucagon when glucocorticoid is administered concurrently with the latter.

Glycogen stores within skeletal muscles can be mobilized by EPI activation of β -adrenergic receptors, GTP-binding proteins (G proteins), which subsequently activates the second messenger, cAMP. The cAMP activates phosphorylase kinase, which in turn leads to conversion of glycogen to glucose-1-phosphate. Phosphorylase kinase also can be activated by the second messenger, calcium, through the breakdown of phosphatidylinositol phosphate, which is the case in vasopressin-mediated hepatic glycogenolysis.¹³⁸

Glucose Transport and Signaling. Hydrophobic cell membranes are relatively impermeable to hydrophilic glucose molecules. There are two distinct classes of membrane glucose transporters in human systems. These are the facilitated diffusion glucose transporters (GLUTs) that permit the transport of glucose down a concentration gradient (Table 2-9) and the Na⁺/glucose secondary active transport system (SGLT), which transports glucose molecules against concentration gradients by active transport.

Numerous functional human GLUTs have been cloned since 1985. GLUT1 is expressed at its highest level in human erythrocytes, where it may function to increase the glucose carrying capacity of the blood. It is expressed on several other tissues, but little is found in the liver and skeletal muscle. GLUT1 plays a critical role in cerebral glucose uptake as the major GLUT isoform that is constitutively expressed by the endothelium in the blood-brain barrier. GLUT2 is the major glucose transporter of hepatocytes. It is also expressed by intestinal absorptive cells, pancreatic β -cells, renal tubule cells, and insulin-secreting β -cells of the pancreas. GLUT2 is important for glucose uptake and release in the fed and fasted states. GLUT3 is highly expressed in neuronal tissue of the brain and appears to be important to neuronal glucose uptake. GLUT4 is significant to human metabolism because it is the primary glucose transporter of insulin-sensitive tissues, adipose tissue, and skeletal and cardiac muscle. Under basal conditions, these transporters are usually packaged as intracellular vesicles, but when insulin levels rise, rapid translocation of these vesicles to the cell surface occurs, increasing glucose uptake and metabolism in these tissues and preventing chronic elevations in blood glucose levels.

Table 2-9 Human facilitated diffusion glucose transporter (GLUT) family		
TYPE	AMINO ACIDS	MAJOR EXPRESSION SITES
GLUT1	492	Placenta, brain, kidney, colon
GLUT2	524	Liver, pancreatic β -cells, kidney, small intestine
GLUT3	496	Brain, testis
GLUT4	509	Skeletal muscle, heart muscle, brown and white fat
GLUT5	501	Small intestine, sperm

A defect in this insulin-mediated translocation of GLUT4 to the plasma membrane causes peripheral insulin resistance. GLUT4 therefore plays a critical role in the regulation of whole-body glucose homeostasis. GLUT5 has been identified in several tissues but is primarily expressed in the jejunum. Although it possesses some capacity for glucose transport, it is predominantly a fructose transporter.¹³⁹

SGLTs are distinct glucose transport systems found in the intestinal epithelium and in the proximal renal tubules. These systems transport both sodium and glucose intracellularly, and glucose affinity for this transporter increases when sodium ions are attached. SGLT1 is prevalent on brush borders of small intestine enterocytes and primarily mediates the active uptake of luminal glucose. In addition, SGLT1 within the intestinal lumen also enhances gut retention of water through osmotic absorption. SGLT1 and SGLT2 are both associated with glucose reabsorption at proximal renal tubules.

Protein and Amino Acid Metabolism

The average protein intake in healthy young adults ranges from 80 to 120 g/d, and every 6 g of protein yields approximately 1 g of nitrogen. The degradation of 1 g of protein yields approximately 4 kcal of energy, similar to the yield in carbohydrate metabolism.

After injury, the initial systemic proteolysis, mediated primarily by glucocorticoids, increases urinary nitrogen excretion to levels in excess of 30 g/d, which roughly corresponds to a loss in lean body mass of 1.5% per day. An injured individual who does not receive nutrition for 10 days can theoretically lose 15% lean body mass. Therefore, amino acids cannot be considered a long-term fuel reserve, and indeed excessive protein depletion (i.e., 25% to 30% of lean body weight) is not compatible with sustaining life.¹⁴⁰

Protein catabolism after injury provides substrates for gluconeogenesis and for the synthesis of acute-phase proteins. Radiolabeled amino acid incorporation studies and protein analyses confirm that skeletal muscles are preferentially depleted acutely after injury, whereas visceral tissues (e.g., the liver and kidney) remain relatively preserved. The accelerated urea excretion after injury also is associated with the excretion of intracellular elements such as sulfur, phosphorus, potassium, magnesium, and creatinine. Conversely, the rapid utilization of elements such as potassium and magnesium during recovery from major injury may indicate a period of tissue healing.

The net changes in protein catabolism and synthesis correspond to the severity and duration of injury (Fig. 2-23). Elective operations and minor injuries result in lower protein synthesis and moderate protein breakdown. Severe trauma, burns, and sepsis are associated with increased protein catabolism. The rise in urinary nitrogen and negative nitrogen balance can be detected early after injury and peak by 7 days. This state of protein catabolism may persist for as long as 3 to 7 weeks. The patient's prior physical status and age appear to influence the degree of proteolysis after injury or sepsis. Activation of the ubiquitin-proteasome system in muscle cells is one of the major pathways for protein degradation during acute injury. This response is accentuated by tissue hypoxia, acidosis, insulin resistance, and elevated glucocorticoid levels.

NUTRITION IN THE SURGICAL PATIENT

The goal of nutritional support in the surgical patient is to prevent or reverse the catabolic effects of disease or injury. Although several important biologic parameters have been used

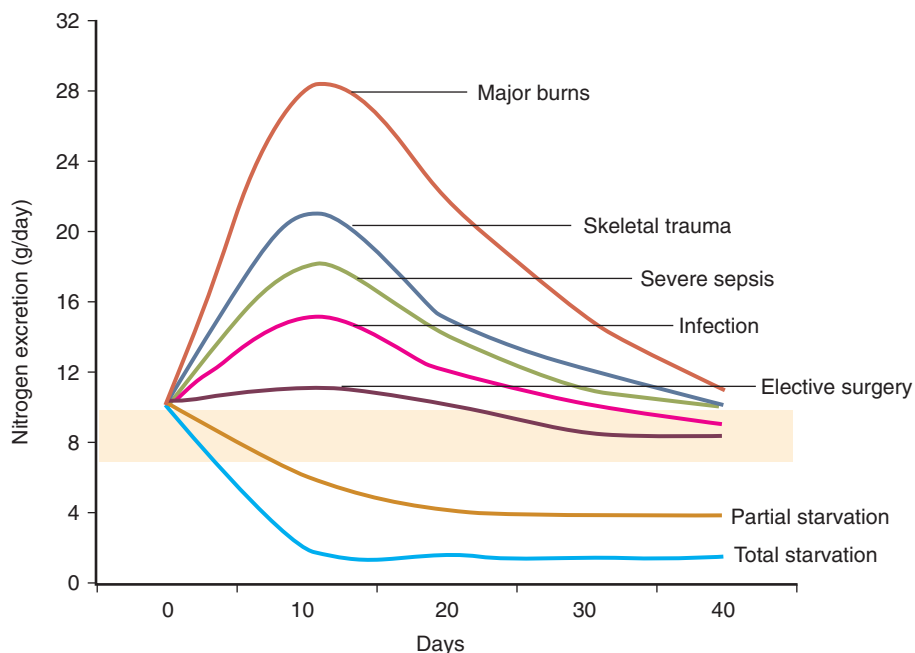


Figure 2-23. The effect of injury severity on nitrogen wasting. (From Long CL, Schaffel N, Geiger J, et al. *Metabolic response to injury and illness: estimation of energy and protein needs from indirect calorimetry and nitrogen balance*. JPEN J Parenter Enteral Nutr. 1979;3(6):452. Copyright © 1979 by A.S.P.E.N. Reprinted by permission of Sage Publications.)

to measure the efficacy of nutritional regimens, the ultimate validation for nutritional support in surgical patients should be improvement in clinical outcome and restoration of function.

Estimation of Energy Requirements

Overall nutritional assessment is undertaken to determine the severity of nutrient deficiencies or excess and to aid in predicting nutritional requirements. Pertinent information is obtained by determining the presence of weight loss, chronic illnesses, or dietary habits that influence the quantity and quality of food intake. Social habits predisposing to malnutrition and the use of medications that may influence food intake or urination should also be investigated. Physical examination seeks to assess loss of muscle and adipose tissues, organ dysfunction, and subtle changes in skin, hair, or neuromuscular function reflecting frank or impending nutritional deficiency. Anthropometric data (i.e., weight change, skinfold thickness, and arm circumference muscle area) and biochemical determinations (i.e., creatinine excretion, albumin level, prealbumin level, total lymphocyte count, and transferrin level) may be used to substantiate the patient's history and physical findings. However, it is imprecise to rely on any single or fixed combination of the findings to accurately assess nutritional status or morbidity. Appreciation for the stresses and natural history of the disease process, in combination with nutritional assessment, remains the basis for identifying patients in acute or anticipated need of nutritional support.

A fundamental goal of nutritional support is to meet the energy requirements for essential metabolic processes and tissue repair. Failure to provide adequate nonprotein energy sources will lead to consumption of lean tissue stores. The requirement for energy may be measured by indirect calorimetry and trends in serum markers (e.g., prealbumin level) and estimated from urinary nitrogen excretion, which is proportional to resting energy expenditure.¹³⁸ However, the use of indirect calorimetry, particularly in the critically ill patient, is labor intensive and often leads to overestimation of caloric requirements.

Basal energy expenditure (BEE) may also be estimated using the Harris-Benedict equations:

$$\text{BEE (men)} = 66.47 + 13.75 (W) + 5.0 (H) - 6.76 (A) \text{ kcal/d}$$

$$\text{BEE (women)} = 655.1 + 9.56 (W) + 1.85 (H) - 4.68 (A) \text{ kcal/d}$$

where W = weight in kilograms; H = height in centimeters; and A = age in years.

These equations, adjusted for the type of surgical stress, are suitable for estimating energy requirements in the majority of hospitalized patients. It has been demonstrated that the provision of 30 kcal/kg per day will adequately meet energy requirements in most postsurgical patients, with a low risk of overfeeding. After trauma or sepsis, energy substrate demands are increased, necessitating greater nonprotein calories beyond calculated energy expenditure (Table 2-10). These additional nonprotein calories provided after injury are usually 1.2 to 2.0 times greater than calculated resting energy expenditure, depending on the type of injury. It is seldom appropriate to exceed this level of nonprotein energy intake during the height of the catabolic phase.

The second objective of nutritional support is to meet the substrate requirements for protein synthesis. An appropriate nonprotein-calorie:nitrogen ratio of 150:1 (e.g., 1 g N = 6.25 g protein) should be maintained, which is the basal calorie requirement provided to limit the use of protein as an energy source. There is now greater evidence suggesting that increased protein intake and a lower calorie:nitrogen ratio of 80:1 to 100:1 may benefit healing in selected hypermetabolic or critically ill patients. In the absence of severe renal or hepatic dysfunction precluding the use of standard nutritional regimens, approximately 0.25 to 0.35 g of nitrogen per kilogram of body weight should be provided daily.¹⁴¹

Vitamins and Minerals

The requirements for vitamins and essential trace minerals usually can be met easily in the average patient with an

Table 2-10

Caloric adjustments above basal energy expenditure (BEE) in hypermetabolic conditions

CONDITION	kcal/kg PER DAY	ADJUSTMENT ABOVE BEE	GRAMS OF PROTEIN/ kg PER DAY	NONPROTEIN CALORIES: NITROGEN
Normal/moderate malnutrition	25–30	1.1	1.0	150:1
Mild stress	25–30	1.2	1.2	150:1
Moderate stress	30	1.4	1.5	120:1
Severe stress	30–35	1.6	2.0	90–120:1
Burns	35–40	2.0	2.5	90–100:1

uncomplicated postoperative course. Therefore, vitamins usually are not given in the absence of preoperative deficiencies. Patients maintained on elemental diets or parenteral hyperalimentation require complete vitamin and mineral supplementation. Commercial enteral diets contain varying amounts of essential minerals and vitamins. It is necessary to ensure that adequate replacement is available in the diet or by supplementation. Numerous commercial vitamin preparations are available for intravenous or intramuscular use, although most do not contain vitamin K and some do not contain vitamin B₁₂ or folic acid. Supplemental trace minerals may be given intravenously via commercial preparations. Essential fatty acid supplementation also may be necessary, especially in patients with depletion of adipose stores.

Overfeeding

Overfeeding usually results from overestimation of caloric needs, as occurs when actual body weight is used to calculate the BEE in patient populations such as the critically ill with significant fluid overload and the obese. Indirect calorimetry can be used to quantify energy requirements but frequently overestimates BEE by 10% to 15% in stressed patients, particularly if they are receiving ventilatory support. In these instances, estimated dry weight should be obtained from preinjury records or family members. Adjusted lean body weight also can be calculated. Overfeeding may contribute to clinical deterioration via increased oxygen consumption, increased carbon dioxide production and prolonged need for ventilatory support, fatty liver, suppression of leukocyte function, hyperglycemia, and increased risk of infection.

ENTERAL NUTRITION

Rationale for Enteral Nutrition

Enteral nutrition generally is preferred over parenteral nutrition based on the lower cost of enteral feeding and the associated risks of the intravenous route, including vascular access complications.¹⁴² Of further consideration are the consequences of gastrointestinal tract disuse, which include diminished secretory IgA production and cytokine production as well as bacterial overgrowth and altered mucosal defenses. For example, laboratory models have long demonstrated that luminal nutrient contact reduces intestinal mucosal atrophy compared with parenteral or no nutritional support.

The benefits of enteral feeding in patients undergoing elective surgery appear to be linked to their preoperative

nutritional status. Studies comparing postoperative enteral and parenteral nutrition in patients undergoing gastrointestinal surgery have demonstrated reduced infectious complications and acute-phase protein production in those fed by the enteral route. Yet prospectively randomized studies of patients with adequate nutritional status (albumin ≥ 4 g/dL) undergoing gastrointestinal surgery demonstrate no differences in outcome and complications between those administered enteral nutrition and those given maintenance intravenous fluids alone in the initial days after surgery.¹⁴³ Furthermore, intestinal permeability studies in well-nourished patients undergoing upper gastrointestinal cancer surgery demonstrated normalization of intestinal permeability and barrier function by the fifth postoperative day.¹⁴⁴ The data for critically ill or injured patients are more definitive as to the benefits of enteral nutrition. Meta-analysis of studies involving critically ill patients demonstrates a 44% reduction in infectious complications in those receiving enteral nutritional support compared with those receiving parenteral nutrition. Most prospectively randomized studies in patients with severe abdominal and thoracic trauma demonstrate significant reductions in infectious complications in patients given early enteral nutrition compared with those who were unfed or received parenteral nutrition. In critically ill patients, prospective studies have also demonstrated that early enteral nutrition is associated with better small-intestinal carbohydrate absorption, shorter duration of mechanical ventilation, and shorter time in the intensive care

6► unit. The exception has been in studies of patients with closed-head injury, in whom no significant differences in outcome were demonstrated between early jejunal feeding and other nutritional support modalities. Moreover, early gastric feeding after closed-head injury was frequently associated with underfeeding and calorie deficiency due to the difficulties in overcoming gastroparesis and the high risk of aspiration. While current evidence remains inconclusive about the benefits of “early” (as defined by feeding in the first 24 hours) versus “late” (as defined by feeding >24 hours after burn) enteral nutrition in burn patients as to its impact on mortality rates, there is reason to believe that early enteral nutrition may positively modulate the initial hypermetabolic response and help to maintain mucosal immunity.

In summary, enteral nutrition is preferred for most critically ill patients—an evidence-based practice supported by clinical data involving a variety of critically ill patient populations, including those with trauma, burns, head injury, major surgery, and acute pancreatitis. For intensive care unit 7► patients who are hemodynamically stable and have a

functioning gastrointestinal tract, early enteral feeding (within 24 to 48 hours of arrival in the intensive care unit) has become a recommended standard of care.¹⁴⁵ For patients undergoing elective surgery, healthy patients without malnutrition who are undergoing uncomplicated surgery can tolerate 10 days of partial starvation (i.e., maintenance intravenous fluids only) before any clinically significant protein catabolism occurs. Earlier intervention is likely indicated for patients in whom preoperative protein-calorie malnutrition has been identified. Other clinical scenarios for which the benefits of enteral nutritional support have been substantiated include permanent neurologic impairment, oropharyngeal dysfunction, short-bowel syndrome, and bone marrow transplantation.

Initiation of enteral nutrition should occur immediately after adequate resuscitation, most readily determined by adequate urine output. The presence of bowel sounds and the passage of flatus or stool are not absolute prerequisites for initiation of enteral nutrition, but in the setting of gastroparesis, feedings should be administered distal to the pylorus. Gastric residuals of 200 mL or more in a 4- to 6-hour period or abdominal distention requires cessation of feeding and adjustment of the infusion rate. Concomitant gastric decompression with distal small-bowel feedings may be appropriate in certain patients such as closed-head injury patients with gastroparesis. There is no evidence to support withholding enteric feedings for patients after bowel resection or for those with low-output enterocutaneous fistulas of <500 mL/d. In fact, a recent systematic review of studies of early enteral feeding (within 24 hours of gastrointestinal surgery) showed no effect on anastomotic leak and a reduction in mortality. Early enteral feeding is also associated with reduced incidence of fistula formation in patients with open abdomen. Enteral feeding should also be offered to patients with short-bowel syndrome or clinical malabsorption, but necessary calories, essential minerals, and vitamins should be supplemented using parenteral modalities.

Hypocaloric Enteral Nutrition

As noted earlier, critically ill and/or injured patients demonstrate increased resting energy expenditure associated with altered metabolism. While several methods exist to predict the energy requirement, the recommended caloric dose for critically ill patients varies, ranging from 25 to 30 kcal/kg. The perceived benefit of achieving the caloric target is to meet the patient's energy needs and to avoid the loss of lean body mass. However, recent evidence supports the idea of caloric restriction, attributing its benefits to improved cellular function in terms of effects on mitochondrial free radical generation, the plasma membrane redox system, and insulin sensitivity. Further support was offered by a single-center, randomized controlled trial that compared permissive underfeeding with target enteral feeding (caloric goal: 60% to 70% compared with 90% to 100% of calculated requirement) in critically ill medical and surgical patients.¹⁴⁶ This study demonstrated that permissive underfeeding was associated with lower mortality and morbidity than was target feeding. However, current guidelines do not recommend hypocaloric feeding without confirmation of these data from the multicenter trial that is currently ongoing. A recent study examined the use of trophic feedings in patients with acute lung injury. Trophic feedings refer to providing a minimal amount of enteral feedings, which are presumed to have beneficial effects despite not meeting daily caloric needs. When the trophic feeding group (enteral feeding at 10 mL/h) was compared with the

full-feeding group (25 mL/h) over the first 6 days of feeding, there was no improvement in ventilator-free days, 60-day mortality, or infectious complications.¹⁴⁷

Enteral Formulas

For most critically ill patients, the choice of enteral formula will be determined by a number of factors and will include a clinical judgment as to the "best fit" for the patients' needs. In general, feeding formulas to consider are gastrointestinal tolerance-promoting, anti-inflammatory, immune-modulating, organ supportive, and standard enteral nutrition. In addition, guidelines from professional nutrition societies identify certain populations of patients who can benefit from formulations with specific pharmaconutrients.¹⁴⁸ For many others, each physician must use his or her own clinical judgment about what formula will best meet the patient's needs.

The functional status of the gastrointestinal tract determines the type of enteral solutions to be used. Patients with an intact gastrointestinal tract will tolerate complex solutions, but patients who have not been fed via the gastrointestinal tract for prolonged periods are less likely to tolerate complex carbohydrates. In those patients who are having difficulty tolerating standard enteral formulas, peptide- and MCT-based formulas with prebiotics can lessen gastrointestinal tolerance problems. Additionally, in patients with demonstrated malabsorption issues, such as with inflammatory bowel diseases or short-bowel syndrome, current guidelines endorse the provision of hydrolyzed protein formulas to improve absorption. Guidelines have not yet been made with regard to the fiber content of enteral formulas. However, recent evidence indicates that supplementation of enteral formulas with soluble dietary fiber may be beneficial for improving stool consistency in patients suffering from diarrhea.

Factors that influence the choice of enteral formula also include the extent of organ dysfunction (e.g., renal, pulmonary, hepatic, or gastrointestinal), the nutrients needed to restore optimal function and healing, and the cost of specific products. There are still no conclusive data to recommend one category of product over another, and nutritional support committees typically develop the most cost-efficient enteral formula for the most commonly encountered disease categories within the institution.

As discussed extensively in the first sections of this chapter, surgery and trauma result in a significant "sterile" inflammatory response that impacts the innate and adaptive immune systems. The provision of immune-modulating nutrients, termed "immunonutrition," is one mechanism by which the immune response can be supported and an attempt made to lower infectious risk. At present, the best-studied immunonutrients are glutamine, arginine, and ω -3 PUFAs.

"Immunonutrients." Glutamine is the most abundant amino acid in the human body, comprising nearly two thirds of the free intracellular amino acid pool. Of this, 75% is found within the skeletal muscles. In healthy individuals, glutamine is considered a nonessential amino acid, because it is synthesized within the skeletal muscles and the lungs. Glutamine is a necessary substrate for nucleotide synthesis in most dividing cells and hence provides a major fuel source for enterocytes. It also serves as an important fuel source for immunocytes such as lymphocytes and macrophages and is a precursor for glutathione, a major intracellular antioxidant. During stress states such as sepsis, or in tumor-bearing hosts, peripheral glutamine stores are rapidly depleted, and the amino acid is preferentially shunted as a fuel

source toward the visceral organs and tumors, respectively.¹⁴⁹ These situations create, at least experimentally, a glutamine-depleted environment, with consequences including enterocyte and immunocyte starvation. Glutamine metabolism during stress in humans, however, may be more complex than is indicated in previously reported animal data. Although it is hypothesized that provision of glutamine may preserve immune cell and enterocyte function and enhance nitrogen balance during injury or sepsis, the clinical outcome is very strongly dependent on the patient population, as will be discussed later.

Arginine, also a nonessential amino acid in healthy subjects, first attracted attention for its immunoenhancing properties, wound-healing benefits, and association with improved survival in animal models of sepsis and injury.¹⁵⁰ As with glutamine, the benefits of experimental arginine supplementation during stress states are diverse. In clinical studies involving critically ill and injured patients and patients who have undergone surgery for certain malignancies, enteral administration of arginine has led to net nitrogen retention and protein synthesis, whereas isonitrogenous diets have not. Some of these studies also provide *in vitro* evidence of enhanced immunocyte function. The clinical utility of arginine supplementation in improving overall patient outcome remains an area of investigation.

As previously discussed, ω -3 PUFAs (canola oil or fish oil) displace ω -6 fatty acids in cell membranes, which theoretically reduces the proinflammatory response from prostaglandin production. Hence, there has been significant interest in reducing the ratio of ω -6 to ω -3 fatty acids.

Low-Residue Isotonic Formulas. Most low-residue isotonic formulas provide a caloric density of 1.0 kcal/mL, and approximately 1500 to 1800 mL are required to meet daily requirements. These low-osmolality compositions provide baseline carbohydrates, protein, electrolytes, water, fat, and fat-soluble vitamins (some do not have vitamin K) and typically have a nonprotein-calorie:nitrogen ratio of 150:1. These contain no fiber bulk and therefore leave minimum residue. These solutions usually are considered to be the standard or first-line formulas for stable patients with an intact gastrointestinal tract.

Isotonic Formulas with Fiber. Isotonic formulas with fiber contain soluble and insoluble fiber, which is most often soy based. Physiologically, fiber-based solutions delay intestinal transit time and may reduce the incidence of diarrhea compared with nonfiber solutions. Fiber stimulates pancreatic lipase activity and is degraded by gut bacteria into short-chain fatty acids (SCFAs), an important fuel for colonocytes. Recent data have also demonstrated the expression of SCFA receptors on leukocytes, suggesting that fiber fermentation by the colonic microbiome may indirectly regulate immune cell function. Future work in this area is likely to demonstrate important links between fiber type, microbiome composition, and immune health.

Immune-Enhancing Formulas. Immune-enhancing formulas are fortified with special nutrients that are purported to enhance various aspects of immune or solid organ function. Such additives include glutamine, arginine, ω -3 fatty acids, and nucleotides.¹⁵¹ Although several trials have proposed that one or more of these additives reduce surgical complications and improve outcome, these results have not been uniformly corroborated by other trials. The Canadian Clinical Practice Guidelines currently do not recommend the addition of arginine supplements for critically ill patients due to the potential for harm when used in septic patients.¹⁵² With regard to ω -3 PUFAs, results from

the EDEN-Omega study demonstrated that twice-daily enteral supplementation of ω -3 fatty acids, α -linolenic acid, and antioxidants did not improve the primary endpoint of ventilator-free days or other clinical outcomes in patients with acute lung injury and may be harmful.¹⁵³ Glutamine supplementation should be strictly guided by the individual patient condition. Enteral and parenteral supplementation with glutamine appears to have a harmful effect in critically ill patients with multiorgan failure as evidenced by significantly increased mortality (REDOXS study). However, for burn or trauma patients who are hemodynamically stable and without evidence of organ dysfunction, glutamine supplementation has been shown to be beneficial in terms of decreased LOS and infectious complications.

Calorie-Dense Formulas. The primary distinction of calorie-dense formulas is a greater caloric value for the same volume. Most commercial products of this variety provide 1.5 to 2 kcal/mL and therefore are suitable for patients requiring fluid restriction or those unable to tolerate large-volume infusions. As expected, these solutions have higher osmolality than standard formulas and are suitable for intragastric feedings.

High-Protein Formulas. High-protein formulas are available in isotonic and nonisotonic mixtures and are proposed for critically ill or trauma patients with high protein requirements. These formulas have nonprotein-calorie:nitrogen ratios between 80:1 and 120:1. While some observational studies show improved outcomes with higher protein intakes in critically ill patients, there are limited data from randomized trials, which prevents making strong conclusions about the dose of protein in critically ill patients.

Elemental Formulas. Elemental formulas contain predigested nutrients and provide proteins in the form of small peptides. Complex carbohydrates are limited, and fat content, in the form of MCTs and LCTs, is minimal. The primary advantage of such a formula is ease of absorption, but the inherent scarcity of fat, associated vitamins, and trace elements limits its long-term use as a primary source of nutrients. Due to its high osmolality, dilution or slow infusion rates usually are necessary, particularly in critically ill patients. These formulas have been used frequently in patients with malabsorption, gut impairment, and pancreatitis, but their cost is significantly higher than that of standard formulas. To date, there has been no evidence of their benefit in routine use.

Renal Failure Formulas. The primary benefits of renal formulas are the lower fluid volume and concentrations of potassium, phosphorus, and magnesium needed to meet daily calorie requirements. This type of formulation almost exclusively contains essential amino acids and has a high nonprotein-calorie:nitrogen ratio; however, it does not contain trace elements or vitamins.

Pulmonary Failure Formulas. In pulmonary failure formulas, fat content is usually increased to 50% of the total calories, with a corresponding reduction in carbohydrate content. The goal is to reduce carbon dioxide production and alleviate ventilation burden for failing lungs.

Hepatic Failure Formulas. Close to 50% of the proteins in hepatic failure formulas are branched-chain amino acids (e.g., leucine, isoleucine, and valine). The goal of such a formula is to reduce aromatic amino acid levels and increase the levels of branched-chain amino acids, which can potentially reverse encephalopathy in patients with hepatic failure.¹⁵⁴ The use of

these formulas is controversial, however, because no clear benefits have been proven by clinical trials. Protein restriction should be avoided in patients with end-stage liver disease, because such patients have significant protein-energy malnutrition that predisposes them to additional morbidity and mortality.¹⁵⁵

Access for Enteral Nutritional Support

The available techniques and repertoire for enteral access have provided multiple options for feeding the gut. Presently used methods and preferred indications are summarized in Table 2-11.¹⁵⁶

Nasoenteric Tubes. Nasogastric feeding should be reserved for those with intact mentation and protective laryngeal reflexes to minimize risks of aspiration. Even in intubated patients, nasogastric feedings often can be recovered from tracheal suction. Nasojejunal feedings are associated with fewer pulmonary complications including risk of pneumonia, but access past the pylorus requires greater effort to accomplish. Therefore, routine use of small-bowel feedings is preferred in units where small-bowel access is readily feasible. Where there may be difficulties obtaining access, small-bowel feedings may be considered a priority for those patients at high risk for intolerance to enteral nutrition (e.g., high gastric residuals).

Blind insertion of nasogastric feeding tubes is fraught with misplacement, and air instillation with auscultation is inaccurate for ascertaining proper positioning. Radiographic confirmation is usually required to verify the position of the nasogastric feeding tube.

Several methods have been recommended for the passage of nasoenteric feeding tubes into the small bowel, including use of prokinetic agents, right lateral decubitus positioning, gastric insufflation, tube angulation, and application of clockwise torque. However, the successful placement of feeding tubes by these methods is highly variable and operator dependent.

Furthermore, it is time consuming, and success rates for intubation past the duodenum into the jejunum by these methods are <20%. Fluoroscopy-guided intubation past the pylorus has a >90% success rate, and more than half of these intubations result in jejunal placement. Similarly, endoscopy-guided placement past the pylorus has high success rates, but attempts to advance the tube beyond the second portion of the duodenum using a standard gastroduodenoscope are unlikely to be successful.

Small-bowel feeding is more reliable for delivering nutrition than nasogastric feeding. Furthermore, the risks of aspiration pneumonia can be reduced by 25% with small-bowel feeding compared with nasogastric feeding. The disadvantages of the use of nasoenteric feeding tubes are clogging, kinking, and inadvertent displacement or removal of the tube and nasopharyngeal complications. If nasoenteric feeding will be required for longer than 30 days, access should be converted to a percutaneous one.¹⁵⁷

Percutaneous Endoscopic Gastrostomy. The most common indications for percutaneous endoscopic gastrostomy (PEG) include impaired swallowing mechanisms, oropharyngeal or esophageal obstruction, and major facial trauma. It is frequently used for debilitated patients requiring caloric supplementation, hydration, or frequent medication dosing. It is also appropriate for patients requiring passive gastric decompression. Relative contraindications for PEG placement include ascites, coagulopathy, gastric varices, gastric neoplasm, and lack of a suitable abdominal site. Most tubes are 18F to 28F in size and may be used for 12 to 24 months.

Identification of the PEG site requires endoscopic transillumination of the anterior stomach against the abdominal wall. A 14-gauge angiocatheter is passed through the abdominal wall into the fully insufflated stomach. A guidewire is threaded through the angiocatheter, grasped by snares or forceps, and

Table 2-11

Options for enteral feeding access

ACCESS OPTION	COMMENTS
Nasogastric tube	Short-term use only; aspiration risks; nasopharyngeal trauma; frequent dislodgment
Nasoduodenal/nasojejunal tube	Short-term use; lower aspiration risks in jejunum; placement challenges (radiographic assistance often necessary)
Percutaneous endoscopic gastrostomy (PEG)	Endoscopy skills required; may be used for gastric decompression or bolus feeds; aspiration risks; can last 12–24 mo; slightly higher complication rates with placement and site leaks
Surgical gastrostomy	Requires general anesthesia and small laparotomy; procedure may allow placement of extended duodenal/jejunal feeding ports; laparoscopic placement possible
Fluoroscopic gastrostomy	Blind placement using needle and T-prongs to anchor to stomach; can thread smaller catheter through gastrostomy into duodenum/jejunum under fluoroscopy
PEG-jejunal tube	Jejunal placement with regular endoscope is operator dependent; jejunal tube often dislodges retrograde; two-stage procedure with PEG placement, followed by fluoroscopic conversion with jejunal feeding tube through PEG
Direct percutaneous endoscopic jejunostomy (DPEJ)	Direct endoscopic tube placement with enteroscope; placement challenges; greater injury risks
Surgical jejunostomy	Commonly carried out during laparotomy; general anesthesia; laparoscopic placement usually requires assistant to thread catheter; laparoscopy offers direct visualization of catheter placement
Fluoroscopic jejunostomy	Difficult approach with injury risks; not commonly done

pulled out through the mouth. The tapered end of the PEG tube is secured to the guidewire and is pulled into position out of the abdominal wall. The PEG tube is secured without tension against the abdominal wall, and many have reported using the tube within hours of placement. It has been the practice of some to connect the PEG tube to a drainage bag for passive decompression for 24 hours before use, allowing more time for the stomach to seal against the peritoneum.

If endoscopy is not available or technical obstacles preclude PEG placement, the interventional radiologist can attempt the procedure percutaneously under fluoroscopic guidance by first insufflating the stomach against the abdominal wall with a nasogastric tube. If this also is unsuccessful, surgical gastrostomy tube placement can be considered, particularly with minimally invasive methods. When surgery is contemplated, it may be wise to consider directly accessing the small bowel for nutrition delivery.

Although PEG tubes enhance nutritional delivery, facilitate nursing care, and are superior to nasogastric tubes, serious complications occur in approximately 3% of patients. These complications include wound infection, necrotizing fasciitis, peritonitis, aspiration, leaks, dislodgment, bowel perforation, enteric fistulas, bleeding, and aspiration pneumonia.¹⁵⁸ For patients with significant gastroparesis or gastric outlet obstruction, feedings through PEG tubes are hazardous. In such cases, the PEG tube can be used for decompression and allow access for converting the PEG tube to a transpyloric feeding tube.

Percutaneous Endoscopic Gastrostomy-Jejunostomy and Direct Percutaneous Endoscopic Jejunostomy. Although gastric bolus feedings are more physiologic, patients who cannot tolerate gastric feedings or who have significant aspiration risks should be fed directly past the pylorus. In the percutaneous endoscopic gastrostomy-jejunostomy (PEG-J) method, a 9F to 12F tube is passed through an existing PEG tube, past the pylorus, and into the duodenum. This can be achieved by endoscopic or fluoroscopic guidance. With weighted catheter tips and guidewires, the tube can be further advanced past the ligament of Treitz. However, the incidence of long-term PEG-J tube malfunction has been reported to be >50% as a result of retrograde tube migration into the stomach, kinking, or clogging.

Direct percutaneous endoscopic jejunostomy (DPEJ) tube placement uses the same techniques as PEG tube placement but requires an enteroscope or colonoscope to reach the jejunum. DPEJ tube malfunctions are probably less frequent than PEG-J tube malfunctions, and kinking or clogging is usually averted by placement of larger-caliber catheters. The success rate of DPEJ tube placement is variable because of the complexity of endoscopic skills required to locate a suitable jejunal site. In such cases where endoscopic means are not feasible, surgical jejunostomy tube placement is more appropriate, especially when minimally invasive techniques are available.

Surgical Gastrostomy and Jejunostomy. For a patient undergoing complex abdominal or trauma surgery, thought should be given during surgery to the possible routes for subsequent nutritional support, because laparotomy affords direct access to the stomach or small bowel. The only absolute contraindication to feeding jejunostomy is distal intestinal obstruction. Relative contraindications include severe edema of the intestinal wall, radiation enteritis, inflammatory bowel disease, ascites, severe immunodeficiency, and bowel ischemia. Needle-catheter jejunostomies also can be done with a minimal learning curve.

The biggest drawback usually is possible clogging and knotting of the 6F catheter.¹⁵⁹

Abdominal distention and cramps are common adverse effects of early enteral nutrition. Some have also reported impaired respiratory mechanics as a result of intolerance to enteral feedings. These are mostly correctable by temporarily discontinuing feedings and resuming at a lower infusion rate.

Pneumatosis intestinalis and small-bowel necrosis are infrequent but significant problems in patients receiving jejunal tube feedings. Several contributing factors have been proposed, including the hyperosmolarity of enteral solutions, bacterial overgrowth, fermentation, and accumulation of metabolic breakdown products. The common pathophysiology is believed to be bowel distention and consequent reduction in bowel wall perfusion. Risk factors for these complications include cardiogenic and circulatory shock, vasopressor use, diabetes mellitus, and chronic obstructive pulmonary disease. Therefore, enteral feedings in the critically ill patient should be delayed until adequate resuscitation has been achieved. As alternatives, diluting standard enteral formula, delaying the progression to goal infusion rates, or using monomeric solutions with low osmolality requiring less digestion by the gastrointestinal tract all have been successfully used.

PARENTERAL NUTRITION

Parenteral nutrition is the continuous infusion of a hyperosmolar solution containing carbohydrates, proteins, fat, and other necessary nutrients through an indwelling catheter inserted into the superior vena cava. To obtain the maximum benefit, the calorie:protein ratio must be adequate (at least 100 to 150 kcal/g nitrogen), and both carbohydrates and proteins must be infused simultaneously. When the sources of calories and nitrogen are given at different times, there is a significant decrease in nitrogen utilization. These nutrients can be given in quantities considerably greater than the basic caloric and nitrogen requirements, and this method has proved to be highly successful in achieving growth and development, positive nitrogen balance, and weight gain in a variety of clinical situations. Clinical trials and meta-analysis of studies of parenteral feeding in the perioperative period have suggested that preoperative nutritional support may benefit some surgical patients, particularly those with extensive malnutrition. Short-term use of parenteral nutrition in critically ill patients (i.e., duration of <7 days) when enteral nutrition may have been instituted is associated with higher rates of infectious complications. After severe injury, parenteral nutrition is associated with higher rates of infectious risks than is enteral feeding (Table 2-12). Clinical studies have demonstrated that parenteral feeding with complete bowel rest results in augmented stress hormone and inflammatory mediator response to an antigenic challenge. However, parenteral feeding still is associated with fewer infectious complications than no feeding at all. In cancer patients, delivery of parenteral nutrition has not been shown to benefit clinical response, prolong survival, or ameliorate the toxic effects of chemotherapy, and infectious complications are increased.

Rationale for Parenteral Nutrition

The principal indications for parenteral nutrition are malnutrition, sepsis, or surgical or traumatic injury in seriously ill patients for whom use of the gastrointestinal tract for feedings is not possible. In some instances, intravenous nutrition may be used to supplement inadequate oral intake. The safe and

Table 2-12

Incidence of septic morbidity in parenterally and enterally fed trauma patients

COMPLICATION	BLUNT TRAUMA		PENETRATING TRAUMA		TOTAL	
	TEN N = 48	TPN N = 44	TEN N = 38	TPN N = 48	TEN N = 44	TPN N = 84
Abdominal abscess	2	1	2	6	4	7
Pneumonia	4	10	1	2	5	12
Wound infection	0	2	3	1	3	3
Bacteremia	1	4	0	1	1	5
Urinary tract	1	1	0	1	1	2
Other	5	4	1	1	6	5
Total complications	13	22	7	12	20	34
% Complications per patient group	27%	50%	18%	30%	23%	39%

Source: Reproduced with permission from Moore FA, Feliciano DV, Andrassy RJ et al. Early enteral feeding, compared with parenteral, reduces postoperative septic complications. *Ann Surg.* 1992;216(2):172-183.

successful use of parenteral nutrition requires proper selection of patients with specific nutritional needs, experience with the technique, and an awareness of the associated complications. In patients with significant malnutrition, parenteral nutrition can rapidly improve nitrogen balance, which may enhance immune function. Routine postoperative use of parenteral nutrition is not shown to have clinical benefit and may be associated with a significant increase in complication rate. As with enteral nutrition, the fundamental goals are to provide sufficient calories and nitrogen substrate to promote tissue repair and to maintain the integrity or growth of lean tissue mass. The following are patient groups for whom parenteral nutrition has been used in an effort to achieve these goals:

1. Newborn infants with catastrophic gastrointestinal anomalies, such as tracheoesophageal fistula, gastroschisis, omphalocele, or massive intestinal atresia
2. Infants who fail to thrive due to gastrointestinal insufficiency associated with short-bowel syndrome, malabsorption, enzyme deficiency, meconium ileus, or idiopathic diarrhea
3. Adult patients with short-bowel syndrome secondary to massive small-bowel resection (<100 cm without colon or ileocecal valve or <50 cm with intact ileocecal valve and colon)
4. Patients with enteroenteric, enterocolic, enterovesical, or high-output enterocutaneous fistulas (>500 mL/d)
5. Surgical patients with prolonged paralytic ileus after major operations (>7 to 10 days), multiple injuries, or blunt or open abdominal trauma, or patients with reflex ileus complicating various medical diseases
6. Patients with normal bowel length but with malabsorption secondary to sprue, hypoproteinemia, enzyme or pancreatic insufficiency, regional enteritis, or ulcerative colitis
7. Adult patients with functional gastrointestinal disorders such as esophageal dyskinesia after cerebrovascular accident, idiopathic diarrhea, psychogenic vomiting, or anorexia nervosa
8. Patients with granulomatous colitis, ulcerative colitis, or tuberculous enteritis in whom major portions of the absorptive mucosa are diseased
9. Patients with malignancy, with or without cachexia, in whom malnutrition might jeopardize successful use of a therapeutic option
10. Patients in whom attempts to provide adequate calories by enteral tube feedings or high residuals have failed
11. Critically ill patients who are hypermetabolic for >5 days or for whom enteral nutrition is not feasible

Patients in whom hyperalimentation is *contraindicated* include the following:

1. Patients for whom a specific goal for patient management is lacking or for whom, instead of extending a meaningful life, inevitable dying would be delayed
2. Patients experiencing hemodynamic instability or severe metabolic derangement (e.g., severe hyperglycemia, azotemia, encephalopathy, hyperosmolality, and fluid-electrolyte disturbances) requiring control or correction before hypertonic intravenous feeding is attempted
3. Patients for whom gastrointestinal tract feeding is feasible; in the vast majority of instances, this is the best route by which to provide nutrition
4. Patients with good nutritional status
5. Infants with <8 cm of small bowel, because virtually all have been unable to adapt sufficiently despite prolonged periods of parenteral nutrition
6. Patients who are irreversibly decerebrate or otherwise dehumanized

Total Parenteral Nutrition

Total parenteral nutrition (TPN), also referred to as *central parenteral nutrition*, requires access to a large-diameter vein to deliver the entire nutritional requirements of the individual. Dextrose content of the solution is high (15% to 25%), and all other macronutrients and micronutrients are deliverable by this route.

Peripheral Parenteral Nutrition

The lower osmolality of the solution used for peripheral parenteral nutrition (PPN), secondary to reduced levels of dextrose (5% to 10%) and protein (3%), allows its administration

via peripheral veins. Some nutrients cannot be supplemented because they cannot be concentrated into small volumes. Therefore, PPN is not appropriate for repleting patients with severe malnutrition. It can be considered if central routes are not available or if supplemental nutritional support is required. Typically, PPN is used for short periods (<2 weeks). Beyond this time, TPN should be instituted.

Initiation of Parenteral Nutrition

The basic solution for parenteral nutrition contains a final concentration of 15% to 25% dextrose and 3% to 5% crystalline amino acids. The solutions usually are prepared in sterile conditions in the pharmacy from commercially available kits containing the component solutions and transfer apparatus. Preparation in the pharmacy under laminar flow hoods reduces the incidence of bacterial contamination of the solution. Proper preparation with suitable quality control is absolutely essential to avoid septic complications.

The proper provision of electrolytes and amino acids must take into account routes of fluid and electrolyte loss, renal function, metabolic rate, cardiac function, and the underlying disease state.

Intravenous vitamin preparations also should be added to parenteral formulas. Vitamin deficiencies are rare occurrences if such preparations are used. In addition, because vitamin K is not part of any commercially prepared vitamin solution, it should be supplemented on a weekly basis. During prolonged parenteral nutrition with fat-free solutions, essential fatty acid deficiency may become clinically apparent and manifests as dry, scaly dermatitis and loss of hair. The syndrome may be prevented by periodic infusion of a fat emulsion at a rate equivalent to 10% to 15% of total calories. Essential trace minerals may be required after prolonged TPN and may be supplied by direct addition of commercial preparations. The most frequent presentation of trace mineral deficiencies is the eczematoid rash developing both diffusely and at intertriginous areas in zinc-deficient patients. Other rare trace mineral deficiencies include a microcytic anemia associated with copper deficiency and glucose intolerance presumably related to chromium deficiency. The latter complications are seldom seen except in patients receiving parenteral nutrition for extended periods. The daily administration of commercially available trace mineral supplements will obviate most such problems.

Depending on fluid and nitrogen tolerance, parenteral nutrition solutions generally can be increased over 2 to 3 days to achieve the desired infusion rate. Insulin may be supplemented as necessary to ensure glucose tolerance. Administration of additional intravenous fluids and electrolytes may occasionally be necessary in patients with persistently high fluid losses. The patient should be carefully monitored for development of electrolyte, volume, acid-base, and septic complications. Vital signs and urinary output should be measured regularly, and the patient should be weighed regularly. Frequent adjustments of the volume and composition of the solutions are necessary during the course of therapy. Samples for measurement of electrolytes are drawn daily until levels are stable and every 2 or 3 days thereafter. Blood counts, blood urea nitrogen level, levels of liver function indicators, and phosphate and magnesium levels are determined at least weekly.

The urine or capillary blood glucose level is checked every 6 hours, and serum glucose concentration is checked at least once daily during the first few days of the infusion and at frequent

intervals thereafter. Relative glucose intolerance, which often manifests as glycosuria, may occur after initiation of parenteral nutrition. If blood glucose levels remain elevated or glycosuria persists, the dextrose concentration may be decreased, the infusion rate slowed, or regular insulin added to each bottle. The rise in blood glucose concentration observed after initiating parenteral nutrition may be temporary, as the normal pancreas increases its output of insulin in response to the continuous carbohydrate infusion. In patients with diabetes mellitus, additional insulin may be required.

Potassium is essential to achieve positive nitrogen balance and replace depleted intracellular stores. In addition, a significant shift of potassium ion from the extracellular to the intracellular space may take place because of the large glucose infusion, with resultant hypokalemia, metabolic alkalosis, and poor glucose utilization. In some cases as much as 240 mEq of potassium ion daily may be required. Hypokalemia may cause glycosuria, which would be treated with potassium, not insulin. Thus, before giving insulin, the serum potassium level must be checked to avoid exacerbating the hypokalemia.

Patients with insulin-dependent diabetes mellitus may exhibit wide fluctuations in blood glucose levels while receiving parenteral nutrition. This may require protocol-driven intravenous insulin therapy. In addition, partial replacement of dextrose calories with lipid emulsions may alleviate these problems in selected patients.

Lipid emulsions derived from soybean or safflower oils are widely used as an adjunctive nutrient to prevent the development of essential fatty acid deficiency, although recent data support reducing the overall ω -6 PUFA load in favor of ω -3 PUFAs or MCTs. There is no evidence of enhanced metabolic benefit when >10% to 15% of calories are provided as lipid emulsions. Although the administration of 500 mL of 20% fat emulsion one to three times a week is sufficient to prevent essential fatty acid deficiency, it is common to provide fat emulsions on a daily basis to provide additional calories. The triple mix of carbohydrate, fat, and amino acids is infused at a constant rate during a 24-hour period. The theoretical advantages of a constant fat infusion rate include increased efficiency of lipid utilization and reduction in the impairment of reticuloendothelial function normally identified with bolus lipid infusions. The addition of lipids to an infusion bag may alter the stability of some micro-nutrients in a dextrose–amino acid preparation.

The delivery of parenteral nutrition requires central intravenous access. Temporary or short-term access can be achieved with a 16-gauge percutaneous catheter inserted into a subclavian or internal jugular vein and threaded into the superior vena cava. More permanent access with the intention of providing long-term or home parenteral nutrition can be achieved by placement of a catheter with a subcutaneous port for access by tunneling a catheter with a substantial subcutaneous length or threading a long catheter through the basilic or cephalic vein into the superior vena cava.

Complications of Parenteral Nutrition

Technical Complications. One of the more common and serious complications associated with long-term parenteral feeding is sepsis secondary to contamination of the central venous catheter. Contamination of solutions should be also considered but is rare when proper pharmacy protocols have been followed. Central line–associated bloodstream infections (CLABSI) occur as a consequence of hematogenous seeding of the

catheter with bacteria. One of the earliest signs of systemic sepsis from CLA-BSI may be the sudden development of glucose intolerance (with or without temperature increase) in a patient who previously has been maintained on parenteral alimentation without difficulty. When this occurs, or if high fever ($>38.5^{\circ}\text{C}$ [101.3°F]) develops without obvious cause, a diligent search for a potential septic focus is indicated. Other causes of fever should also be investigated. If fever persists, the infusion catheter should be removed and submitted for culture. If the catheter is the cause of the fever, removal of the infectious source is usually followed by rapid defervescence. Some centers are now replacing catheters considered at low risk for infection over a guidewire. However, if blood cultures are positive and the catheter tip is also positive, then the catheter should be removed and placed in a new site. Should evidence of infection persist over 24 to 48 hours without a definable source, the catheter should be replaced into the opposite subclavian vein or into one of the internal jugular veins and the infusion restarted.¹⁶⁰

The use of multilumen catheters may be associated with a slightly increased risk of infection. This is most likely associated with greater catheter manipulation and intensive use. The rate of catheter infection is highest for those placed in the femoral vein, lower for those in the jugular vein, and lowest for those in the subclavian vein. When catheters are indwelling for <3 days, infection risks are negligible. If indwelling time is 3 to 7 days, the infection risk is 3% to 5%. Indwelling times of >7 days are associated with a catheter infection risk of 5% to 10%. Strict adherence to barrier precautions also reduces the rate of infection, as can the implementation of procedure checklists to ensure compliance with evidence-based guidelines shown to reduce infectious risk.¹⁶¹

Other complications related to catheter placement include the development of pneumothorax, hemothorax, hydrothorax, subclavian artery injury, thoracic duct injury, cardiac arrhythmia, air embolism, catheter embolism, and cardiac perforation with tamponade. All of these complications may be avoided by strict adherence to proper techniques. Further, the use of ultrasonographic guidance during central venous line placement has been demonstrated to significantly decrease the failure rate, complication rate, and number of attempts required for successful access.¹⁶²

Metabolic Complications. Hyperglycemia may develop with normal rates of infusion in patients with impaired glucose tolerance or in any patient if the hypertonic solutions are administered too rapidly. This is a particularly common complication in patients with latent diabetes and in patients subjected to severe surgical stress or trauma. Treatment of the condition consists of volume replacement with correction of electrolyte abnormalities and the administration of insulin. This complication can be avoided with careful attention to daily fluid balance and frequent monitoring of blood glucose levels and serum electrolytes.

Increasing experience has emphasized the importance of not overfeeding the parenterally nourished patient. This is particularly true for the depleted patient in whom excess calorie infusion may result in carbon dioxide retention and respiratory insufficiency. In addition, excess feeding also has been related to the development of hepatic steatosis or marked glycogen deposition in selected patients. Cholestasis and formation of gallstones are common in patients receiving long-term parenteral nutrition. Mild but transient abnormalities of serum transaminase, alkaline phosphatase, and bilirubin levels occur in many parenterally nourished patients. Failure of the liver

enzymes to plateau or return to normal over 7 to 14 days should suggest another etiology.

Intestinal Atrophy. Lack of intestinal stimulation is associated with intestinal mucosal atrophy, diminished villous height, bacterial overgrowth, reduced lymphoid tissue size, reduced IgA production, and impaired gut immunity. The full clinical implications of these changes are not well realized, although bacterial translocation has been demonstrated in animal models. The most efficacious method to prevent these changes is to provide at least some nutrients enterally. In patients requiring TPN, it may be feasible to infuse small amounts of feedings via the gastrointestinal tract.

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3 chapter

Fluid and Electrolyte Management of the Surgical Patient

G. Tom Shires III

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INTRODUCTION

Fluid and electrolyte management is paramount to the care of the surgical patient. Changes in both fluid volume and electrolyte composition occur preoperatively, intraoperatively, and postoperatively, as well as in response to trauma and sepsis. The sections that follow review the normal anatomy of body fluids, electrolyte composition and concentration abnormalities and treatments, common metabolic derangements, and alternative resuscitative fluids. These concepts are then discussed in relationship to management of specific surgical patients and their commonly encountered fluid and electrolyte abnormalities.

BODY FLUIDS

Total Body Water

Water constitutes approximately 50% to 60% of total body weight. The relationship between total body weight and total body water (TBW) is relatively constant for an individual and is primarily a reflection of body fat. Lean tissues such as muscle and solid organs have higher water content than fat and bone. As a result, young, lean males have a higher proportion of body weight as water than elderly or obese individuals. Deuterium oxide and tritiated water have been used in clinical research to measure TBW by indicator dilution methods. In an average young adult male, TBW accounts for 60% of total body weight, whereas in an average young adult female, it is 50%.¹ The lower percentage of TBW in females correlates with a higher percentage of adipose tissue and lower percentage of muscle mass in most. Estimates of percentage of TBW should be adjusted downward approximately 10% to 20% for obese individuals and upward by 10% for malnourished individuals. The highest percentage of TBW is found in newborns, with approximately 80%

of their total body weight comprised of water. This decreases to approximately 65% by 1 year of age and thereafter remains fairly constant.

Fluid Compartments

TBW is divided into three functional fluid compartments: plasma, extravascular interstitial fluid, and intracellular fluid (Fig. 3-1). The extracellular fluids (ECF), plasma and interstitial fluid, together compose about one third of the TBW, and the intracellular compartment composes the remaining two thirds. The extracellular water composes 20% of the total body weight and is divided between plasma (5% of body weight) and interstitial fluid (15% of body weight). Intracellular water makes up approximately 40% of an individual's total body weight, with the largest proportion in the skeletal muscle mass. ECF is measured using indicator dilution methods. The distribution volumes of NaBr and radioactive sulfate have been used to measure ECF in clinical research. Measurement of the intracellular compartment is then determined indirectly by subtracting the measured ECF from the simultaneous TBW measurement.

Composition of Fluid Compartments

The normal chemical composition of the body fluid compartments is shown in Fig. 3-2. The ECF compartment is balanced between sodium, the principal cation, and chloride and bicarbonate, the principal anions. The intracellular fluid compartment is composed primarily of the cations potassium and magnesium, and the anions phosphate and sulfate, and proteins. The concentration gradient between compartments is maintained by adenosine triphosphate-driven sodium-potassium pumps located within the cell membranes. The composition of the plasma and interstitial fluid differs only slightly in ionic composition. The slightly higher protein content (organic anions)

Key Points

- 1▶ Proper management of fluid and electrolytes facilitates crucial homeostasis that allows cardiovascular perfusion, organ system function, and cellular mechanisms to respond to surgical illness.
- 2▶ Knowledge of the compartmentalization of body fluids forms the basis for understanding pathologic shifts in these fluid spaces in disease states. Although difficult to quantify, a deficiency in the functional extracellular fluid compartment often requires resuscitation with isotonic fluids in surgical and trauma patients.
- 3▶ Alterations in the concentration of serum sodium have profound effects on cellular function due to water shifts between the intracellular and extracellular spaces.
- 4▶ Different rates of compensation between respiratory and metabolic components of acid-base homeostasis require frequent laboratory reassessment during therapy.
- 5▶ Although active investigation continues, alternative resuscitation fluids have limited clinical utility, other than the correction of specific electrolyte abnormalities.
- 6▶ Most acute surgical illnesses are accompanied by some degree of volume loss or redistribution. Consequently, isotonic fluid administration is the most common initial intravenous fluid strategy, while attention is being given to alterations in concentration and composition.
- 7▶ Some surgical patients with neurologic illness, malnutrition, acute renal failure, or cancer require special attention to well-defined, disease-specific abnormalities in fluid and electrolyte status.

in plasma results in a higher plasma cation composition relative to the interstitial fluid, as explained by the Gibbs-Donnan equilibrium equation. Proteins add to the osmolality of the plasma and contribute to the balance of forces that determine fluid balance across the capillary endothelium. Although the movement of ions and proteins between the various fluid compartments is restricted, water is freely diffusible. Water is distributed evenly throughout all fluid compartments of the body so that a given volume of water increases the volume of any one compartment relatively little. Sodium, however, is confined to the ECF compartment, and because of its osmotic and electrical properties, it remains associated with water. Therefore, sodium-containing fluids are distributed throughout the ECF and add to the volume of both the intravascular and interstitial spaces. Although the administration of sodium-containing fluids expands the intravascular volume, it also expands the interstitial space by approximately three times as much as the plasma.

Osmotic Pressure

The physiologic activity of electrolytes in solution depends on the number of particles per unit volume (millimoles per liter, or mmol/L), the number of electric charges per unit volume

(milliequivalents per liter, or mEq/L), and the number of osmotically active ions per unit volume (milliosmoles per liter, or mOsm/L). The concentration of electrolytes usually is expressed in terms of the chemical combining activity, or equivalents. An equivalent of an ion is its atomic weight expressed in grams divided by the valence:

$$\text{Equivalent} = \text{atomic weight (g)} / \text{valence}$$

For univalent ions such as sodium, 1 mEq is the same as 1 mmol. For divalent ions such as magnesium, 1 mmol equals 2 mEq. The number of milliequivalents of cations must be balanced by the same number of milliequivalents of anions. However, the expression of molar equivalents alone does not allow a physiologic comparison of solutes in a solution.

The movement of water across a cell membrane depends primarily on osmosis. To achieve osmotic equilibrium, water moves across a semipermeable membrane to equalize the concentration on both sides. This movement is determined by the concentration of the solutes on each side of the membrane. Osmotic pressure is measured in units of osmoles (osm) or milliosmoles (mOsm) that refer to the actual number of osmotically

% of Total body weight	Volume of TBW	Male (70 kg)	Female (60 kg)
Plasma 5%	Extracellular volume	14,000 mL	10,000 mL
Interstitial fluid 15%	Plasma	3500 mL	2500 mL
	Interstitial	10,500 mL	7500 mL
Intracellular volume 40%	Intracellular volume	28,000 mL	20,000 mL
		42,000 mL	30,000 mL

Figure 3-1. Functional body fluid compartments. TBW = total body water.

154 mEq/L		154 mEq/L		153 mEq/L		153 mEq/L		200 mEq/L		200 mEq/L	
CATIONS		ANIONS		CATIONS		ANIONS		CATIONS		ANIONS	
Na ⁺	142	Cl ⁻	103	Na ⁺	144	Cl ⁻	114	K ⁺	150	HPO ₄ ³⁻	150
		HCO ₃ ⁻	27							SO ₄ ²⁻	
		SO ₄ ²⁻	3			HCO ₃ ⁻	30			HCO ₃ ⁻	10
		PO ₄ ³⁻				SO ₄ ²⁻	3			Protein	40
K ⁺	4	Organic Acids	5	K ⁺	4	PO ₄ ³⁻		Mg ²⁺	40		
Ca ²⁺	5			Ca ²⁺	3	Organic Acids	5	Na ⁺	10		
Mg ²⁺	3	Protein	16	Mg ²⁺	2	Protein	1				
Plasma				Interstitial fluid				Intracellular fluid			

Figure 3-2. Chemical composition of body fluid compartments.

active particles. For example, 1 mmol of sodium chloride contributes to 2 mOsm (one from sodium and one from chloride). The principal determinants of osmolality are the concentrations of sodium, glucose, and urea (blood urea nitrogen, or BUN):

$$\text{Calculated serum osmolality} = 2 \text{ sodium} + (\text{glucose}/18) + (\text{BUN}/2.8)$$

The osmolality of the intracellular and extracellular fluids is maintained between 290 and 310 mOsm in each compartment. Because cell membranes are permeable to water, any change in osmotic pressure in one compartment is accompanied by a redistribution of water until the effective osmotic pressure between compartments is equal. For example, if the ECF concentration of sodium increases, there will be a net movement of water from the intracellular to the extracellular compartment. Conversely, if the ECF concentration of sodium decreases, water will move into the cells. Although the intracellular fluid shares in losses that involve a change in concentration or composition of the ECF, an isotonic change in volume in either one of the compartments is not accompanied by the net movement of water as long as the ionic concentration remains the same. For practical clinical purposes, most significant gains and losses of body fluid are directly from the extracellular compartment.

BODY FLUID CHANGES

Normal Exchange of Fluid and Electrolytes

The healthy person consumes an average of 2000 mL of water per day, approximately 75% from oral intake and the rest

extracted from solid foods. Daily water losses include 800 to 1200 mL in urine, 250 mL in stool, and 600 mL in insensible losses. Insensible losses of water occur through both the skin (75%) and lungs (25%) and can be increased by such factors as fever, hypermetabolism, and hyperventilation. Sensible water losses such as sweating or pathologic loss of gastrointestinal (GI) fluids vary widely, but these include the loss of electrolytes as well as water (Table 3-1). To clear the products of metabolism, the kidneys must excrete a minimum of 500 to 800 mL of urine per day, regardless of the amount of oral intake.

The typical individual consumes 3 to 5 g of dietary salt per day, with the balance maintained by the kidneys. With hyponatremia or hypovolemia, sodium excretion can be reduced to as little as 1 mEq/d or maximized to as much as 5000 mEq/d to achieve balance except in people with salt-wasting kidneys. Sweat is hypotonic, and sweating usually results in only a small sodium loss. GI losses are isotonic to slightly hypotonic and contribute little to net gain or loss of free water when measured and appropriately replaced by isotonic salt solutions.

Classification of Body Fluid Changes

Disorders in fluid balance may be classified into three general categories: disturbances in (a) volume, (b) concentration, and (c) composition. Although each of these may occur simultaneously, each is a separate entity with unique mechanisms demanding individual correction. Isotonic gain or loss of salt solution results in extracellular volume changes, with little impact on intracellular fluid volume. If free water is added or lost from the ECF, water will pass between the ECF and intracellular fluid until solute concentration or osmolality is equalized between

Table 3-1

Water exchange (60- to 80-kg man)

ROUTES	AVERAGE DAILY VOLUME (mL)	MINIMAL (mL)	MAXIMAL (mL)
H ₂ O gain:			
Sensible:			
Oral fluids	800–1500	0	1500/h
Solid foods	500–700	0	1500
Insensible:			
Water of oxidation	250	125	800
Water of solution	0	0	500
H ₂ O loss:			
Sensible:			
Urine	800–1500	300	1400/h
Intestinal	0–250	0	2500/h
Sweat	0	0	4000/h
Insensible:			
Lungs and skin	600	600	1500

the compartments. Unlike with sodium, the concentration of most other ions in the ECF can be altered without significant change in the total number of osmotically active particles, producing only a compositional change. For instance, doubling the serum potassium concentration will profoundly alter myocardial function without significantly altering volume or concentration of the fluid spaces.

Disturbances in Fluid Balance

Extracellular volume deficit is the most common fluid disorder in surgical patients and can be either acute or chronic. Acute volume deficit is associated with cardiovascular and central nervous system signs, whereas chronic deficits display tissue signs, such as a decrease in skin turgor and sunken eyes, in addition to cardiovascular and central nervous system signs (Table 3-2). Laboratory examination may reveal an elevated blood urea nitrogen level if the deficit is severe enough to reduce glomerular filtration and hemoconcentration. Urine osmolality usually will be higher than serum osmolality, and urine sodium will be low, typically <20 mEq/L. Serum sodium concentration does not necessarily reflect volume status and therefore may be high, normal, or low when a volume deficit is present. The most common cause of volume deficit in surgical patients is a loss of GI fluids (Table 3-3) from nasogastric suction, vomiting, diarrhea, or enterocutaneous fistula. In addition, sequestration secondary to soft tissue injuries, burns, and intra-abdominal processes such as peritonitis, obstruction, or prolonged surgery can also lead to massive volume deficits.

Extracellular volume excess may be iatrogenic or secondary to renal dysfunction, congestive heart failure, or cirrhosis. Both plasma and interstitial volumes usually are increased. Symptoms are primarily pulmonary and cardiovascular (see Table 3-2). In fit patients, edema and hyperdynamic circulation are common and well tolerated. However, the elderly and patients with cardiac disease may quickly develop congestive

heart failure and pulmonary edema in response to only a moderate volume excess.

Volume Control

Volume changes are sensed by both osmoreceptors and baroreceptors. Osmoreceptors are specialized sensors that detect even small changes in fluid osmolality and drive changes in thirst and diuresis through the kidneys.² For example, when plasma osmolality is increased, thirst is stimulated and water consumption increases, although the exact cell mechanism is not known.³ Additionally, the hypothalamus is stimulated to secrete vasopressin, which increases water reabsorption in the kidneys.

Table 3-2

Signs and symptoms of volume disturbances

SYSTEM	VOLUME DEFICIT	VOLUME EXCESS
Generalized	Weight loss	Weight gain
	Decreased skin turgor	Peripheral edema
Cardiac	Tachycardia	Increased cardiac output
	Orthostasis/hypotension	Increased central venous pressure
	Collapsed neck veins	Distended neck veins
Renal		Murmur
	Oliguria	—
	Azotemia	
GI	Ileus	Bowel edema
Pulmonary	—	Pulmonary edema

Table 3-3

Composition of GI secretions

TYPE OF SECRETION	VOLUME (mL/24 h)	Na (mEq/L)	K (mEq/L)	Cl (mEq/L)	HCO ₃ ⁻ (mEq/L)
Stomach	1000–2000	60–90	10–30	100–130	0
Small intestine	2000–3000	120–140	5–10	90–120	30–40
Colon	—	60	30	40	0
Pancreas	600–800	135–145	5–10	70–90	95–115
Bile	300–800	135–145	5–10	90–110	30–40

Together, these two mechanisms return the plasma osmolality to normal. Baroreceptors also modulate volume in response to changes in pressure and circulating volume through specialized pressure sensors located in the aortic arch and carotid sinuses.⁴ Baroreceptor responses are both neural, through sympathetic and parasympathetic pathways, and hormonal, through substances including renin-angiotensin, aldosterone, atrial natriuretic peptide, and renal prostaglandins. The net result of alterations in renal sodium excretion and free water reabsorption is restoration of volume to the normal state.

Concentration Changes

Changes in serum sodium concentration are inversely proportional to TBW. Therefore, abnormalities in TBW are reflected by abnormalities in serum sodium levels.

3▶ Hyponatremia. A low serum sodium level occurs when there is an excess of extracellular water relative to sodium. Extracellular volume can be high, normal, or low (Fig. 3-3). In most cases of hyponatremia, sodium concentration is decreased as a consequence of either sodium depletion or dilution.⁵ Dilutional hyponatremia frequently results from excess extracellular water and therefore is associated with a high extracellular volume status. Excessive oral water intake or iatrogenic intravenous (IV) excess free water administration can cause hyponatremia. Post-operative patients are particularly prone to increased secretion of antidiuretic hormone (ADH), which increases reabsorption of free water from the kidneys with subsequent volume expansion and hyponatremia. This is usually self-limiting in that both hyponatremia and volume expansion decrease ADH secretion. Additionally, a number of drugs can cause water retention and subsequent hyponatremia, such as the antipsychotics and tricyclic antidepressants as well as angiotensin-converting enzyme inhibitors. The elderly are particularly susceptible to drug-induced hyponatremia. Physical signs of volume overload usually are absent, and laboratory evaluation reveals hemodilution. Depletional causes of hyponatremia are associated with either a decreased intake or increased loss of sodium-containing fluids. A concomitant ECF volume deficit is common. Causes include decreased sodium intake, such as consumption of a low-sodium diet or use of enteral feeds, which are typically low in sodium; GI losses from vomiting, prolonged nasogastric suctioning, or diarrhea; and renal losses due to diuretic use or primary renal disease.

Hyponatremia also can be seen with an excess of solute relative to free water, such as with untreated hyperglycemia or mannitol administration. Glucose exerts an osmotic force in the extracellular compartment, causing a shift of water from the

intracellular to the extracellular space. Hyponatremia therefore can be seen when the effective osmotic pressure of the extracellular compartment is normal or even high. When hyponatremia in the presence of hyperglycemia is being evaluated, the corrected sodium concentration should be calculated as follows:

For every 100-mg/dL increment in plasma glucose above normal, the plasma sodium should decrease by 1.6 mEq/L

Lastly, extreme elevations in plasma lipids and proteins can cause pseudohyponatremia, because there is no true decrease in extracellular sodium relative to water.

Signs and symptoms of hyponatremia (Table 3-4) are dependent on the degree of hyponatremia and the rapidity with which it occurred. Clinical manifestations primarily have a central nervous system origin and are related to cellular water intoxication and associated increases in intracranial pressure. Oliguric renal failure also can be a rapid complication in the setting of severe hyponatremia.

A systematic review of the etiology of hyponatremia should reveal its cause in a given instance. Hyperosmolar causes, including hyperglycemia or mannitol infusion and pseudohyponatremia, should be easily excluded. Next, depletional versus dilutional causes of hyponatremia are evaluated. In the absence of renal disease, depletion is associated with low urine sodium levels (<20 mEq/L), whereas renal sodium wasting shows high urine sodium levels (>20 mEq/L). Dilutional causes of hyponatremia usually are associated with hypervolemic circulation. A normal volume status in the setting of hyponatremia should prompt an evaluation for a syndrome of inappropriate secretion of ADH.

Hypernatremia. Hypernatremia results from either a loss of free water or a gain of sodium in excess of water. Like hyponatremia, it can be associated with an increased, normal, or decreased extracellular volume (see Fig. 3-3). Hypervolemic hypernatremia usually is caused either by iatrogenic administration of sodium-containing fluids, including sodium bicarbonate, or mineralocorticoid excess as seen in hyperaldosteronism, Cushing's syndrome, and congenital adrenal hyperplasia. Urine sodium concentration is typically >20 mEq/L, and urine osmolality is >300 mOsm/L. Normovolemic hypernatremia can result from renal causes, including diabetes insipidus, diuretic use, and renal disease, or from nonrenal water loss from the GI tract or skin, although the same conditions can result in hypovolemic hypernatremia. When hypovolemia is present, the urine sodium concentration is <20 mEq/L and urine osmolality

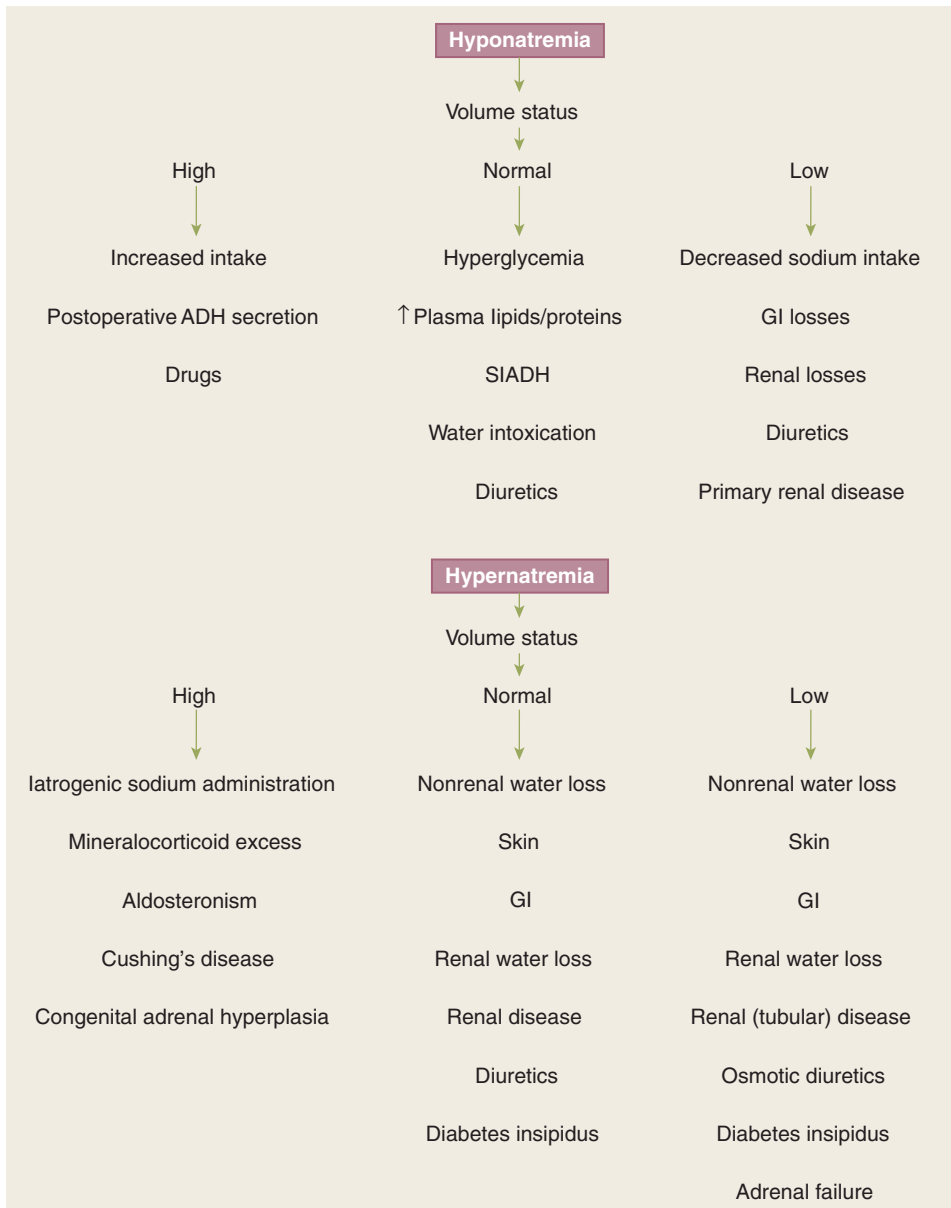


Figure 3-3. Evaluation of sodium abnormalities. ADH = antidiuretic hormone; SIADH = syndrome of inappropriate secretion of antidiuretic hormone.

is <300 to 400 mOsm/L. Nonrenal water loss can occur secondary to relatively isotonic GI fluid losses such as that caused by diarrhea, to hypotonic skin fluid losses such as loss due to fever, or to losses via tracheotomies during hyperventilation. Additionally, thyrotoxicosis can cause water loss, as can the use of hypertonic glucose solutions for peritoneal dialysis. With nonrenal water loss, the urine sodium concentration is <15 mEq/L and the urine osmolarity is >400 mOsm/L.

Symptomatic hypernatremia usually occurs only in patients with impaired thirst or restricted access to fluid, because thirst will result in increased water intake. Symptoms are rare until the serum sodium concentration exceeds 160 mEq/L but, once present, are associated with significant morbidity and mortality. Because symptoms are related to hyperosmolarity, central nervous system effects predominate (see Table 3-4). Water shifts from the intracellular to the extracellular space in response to a hyperosmolar extracellular space, which results in cellular dehydration. This can put traction on the cerebral vessels and lead to subarachnoid hemorrhage. Central nervous system symptoms

can range from restlessness and irritability to seizures, coma, and death. The classic signs of hypovolemic hypernatremia, (tachycardia, orthostasis, and hypotension) may be present, as well as the unique findings of dry, sticky mucous membranes.

Composition Changes: Etiology and Diagnosis

Potassium Abnormalities. The average dietary intake of potassium is approximately 50 to 100 mEq/d, which in the absence of hypokalemia is excreted primarily in the urine. Extracellular potassium is maintained within a narrow range, principally by renal excretion of potassium, which can range from 10 to 700 mEq/d. Although only 2% of the total body potassium ($4.5 \text{ mEq/L} \times 14 \text{ L} = 63 \text{ mEq}$) is located within the extracellular compartment, this small amount is critical to cardiac and neuromuscular function; thus, even minor changes can have major effects on cardiac activity. The intracellular and extracellular distribution of potassium is influenced by a number of factors, including surgical stress, injury, acidosis, and tissue catabolism.

Table 3-4

Clinical manifestations of abnormalities in serum sodium level

BODY SYSTEM	HYPONATREMIA
Central nervous system	Headache, confusion, hyperactive or hypoactive deep tendon reflexes, seizures, coma, increased intracranial pressure
Musculoskeletal	Weakness, fatigue, muscle cramps/twitching
GI	Anorexia, nausea, vomiting, watery diarrhea
Cardiovascular	Hypertension and bradycardia if intracranial pressure increases significantly
Tissue	Lacrimation, salivation
Renal	Oliguria
BODY SYSTEM	HYPERNATREMIA
Central nervous system	Restlessness, lethargy, ataxia, irritability, tonic spasms, delirium, seizures, coma
Musculoskeletal	Weakness
Cardiovascular	Tachycardia, hypotension, syncope
Tissue	Dry sticky mucous membranes, red swollen tongue, decreased saliva and tears
Renal	Oliguria
Metabolic	Fever

Hyperkalemia Hyperkalemia is defined as a serum potassium concentration above the normal range of 3.5 to 5.0 mEq/L. It is caused by excessive potassium intake, increased release of potassium from cells, or impaired potassium excretion by the kidneys (Table 3-5).⁶ Increased intake can be either from oral or IV supplementation, or from red cell lysis after transfusion. Hemolysis, rhabdomyolysis, and crush injuries can disrupt cell membranes and release intracellular potassium into the ECF. Acidosis and a rapid rise in extracellular osmolality from hyperglycemia or IV mannitol can raise serum potassium levels by causing a shift of potassium ions to the extracellular compartment.⁷ Because 98% of total body potassium is in the intracellular fluid compartment, even small shifts of intracellular potassium out of the intracellular fluid compartment can lead to a significant rise in extracellular potassium. A number of medications can contribute to hyperkalemia, particularly in the presence of renal insufficiency, including potassium-sparing diuretics, angiotensin-converting enzyme inhibitors, and non-steroidal anti-inflammatory drugs (NSAIDs). Spironolactone and angiotensin-converting enzyme inhibitors interfere with aldosterone activity, inhibiting the normal renal mechanism of potassium excretion. Acute and chronic renal insufficiency also impairs potassium excretion.

Symptoms of hyperkalemia are primarily GI, neuromuscular, and cardiovascular (Table 3-6). GI symptoms include nausea, vomiting, intestinal colic, and diarrhea. Neuromuscular symptoms range from weakness to ascending paralysis to respiratory failure. Early cardiovascular signs may be apparent from electrocardiogram (ECG) changes and eventually lead

Table 3-5

Etiology of potassium abnormalities**Hyperkalemia****Increased intake**

- Potassium supplementation
- Blood transfusions
- Endogenous load/destruction: hemolysis, rhabdomyolysis, crush injury, gastrointestinal hemorrhage

Increased release

- Acidosis
- Rapid rise of extracellular osmolality (hyperglycemia or mannitol)

Impaired excretion

- Potassium-sparing diuretics
- Renal insufficiency/failure

Hypokalemia**Inadequate intake**

- Dietary, potassium-free intravenous fluids, potassium-deficient TPN

Excessive potassium excretion

- Hyperaldosteronism
- Medications

GI losses

- Direct loss of potassium from GI fluid (diarrhea)
- Renal loss of potassium (to conserve sodium in response to gastric losses)

to hemodynamic symptoms of arrhythmia and cardiac arrest. ECG changes that may be seen with hyperkalemia include high peaked T waves (early), widened QRS complex, flattened P wave, prolonged PR interval (first-degree block), sine wave formation, and ventricular fibrillation.

Hypokalemia Hypokalemia is much more common than hyperkalemia in the surgical patient. It may be caused by inadequate potassium intake; excessive renal potassium excretion; potassium loss in pathologic GI secretions, such as with diarrhea, fistulas, vomiting, or high nasogastric output; or intracellular shifts from metabolic alkalosis or insulin therapy (see Table 3-5). The change in potassium associated with alkalosis can be calculated by the following formula:

Potassium decreases by 0.3 mEq/L for every 0.1 increase in pH above normal.

Additionally, drugs such as amphotericin, aminoglycosides, cisplatin, and ifosfamide that induce magnesium depletion cause renal potassium wastage.^{8,9} In cases in which potassium deficiency is due to magnesium depletion,¹⁰ potassium repletion is difficult unless hypomagnesemia is first corrected.

The symptoms of hypokalemia (see Table 3-6), like those of hyperkalemia, are primarily related to failure of normal contractility of GI smooth muscle, skeletal muscle, and cardiac muscle. Findings may include ileus, constipation, weakness, fatigue, diminished tendon reflexes, paralysis, and cardiac arrest. In the setting of ECF depletion, symptoms may be masked initially and then worsened by further dilution during volume repletion. ECG changes suggestive of hypokalemia include U waves, T-wave flattening, ST-segment changes, and arrhythmias (with digitalis therapy).

Table 3-6

Clinical manifestations of abnormalities in potassium, magnesium, and calcium levels

INCREASED SERUM LEVELS			
SYSTEM	POTASSIUM	MAGNESIUM	CALCIUM
GI	Nausea/vomiting, colic, diarrhea	Nausea/vomiting	Anorexia, nausea/vomiting, abdominal pain
Neuromuscular	Weakness, paralysis, respiratory failure	Weakness, lethargy, decreased reflexes	Weakness, confusion, coma, bone pain
Cardiovascular	Arrhythmia, arrest	Hypotension, arrest	Hypertension, arrhythmia, polyuria
Renal	—	—	Polydipsia
DECREASED SERUM LEVELS			
SYSTEM	POTASSIUM	MAGNESIUM	CALCIUM
GI	Ileus, constipation	—	—
Neuromuscular	Decreased reflexes, fatigue, weakness, paralysis	Hyperactive reflexes, muscle tremors, tetany, seizures	Hyperactive reflexes, paresthesias, carpopedal spasm, seizures
Cardiovascular	Arrest	Arrhythmia	Heart failure

Calcium Abnormalities. The vast majority of the body's calcium is contained within the bone matrix, with <1% found in the ECF. Serum calcium is distributed among three forms: protein bound (40%), complexed to phosphate and other anions (10%), and ionized (50%). It is the ionized fraction that is responsible for neuromuscular stability and can be measured directly. When total serum calcium levels are measured, the albumin concentration must be taken into consideration:

Adjust total serum calcium down by 0.8 mg/dL
for every 1 g/dL decrease in albumin.

Unlike changes in albumin, changes in pH will affect the ionized calcium concentration. Acidosis decreases protein binding, thereby increasing the ionized fraction of calcium.

Daily calcium intake is 1 to 3 g/d. Most of this is excreted via the bowel, with urinary excretion relatively low. Total body calcium balance is under complex hormonal control, but disturbances in metabolism are relatively long term and less important in the acute surgical setting. However, attention to the critical role of ionized calcium in neuromuscular function often is required.

Hypocalcemia Hypocalcemia is defined as a serum calcium level above the normal range of 8.5 to 10.5 mEq/L or an increase in the ionized calcium level above 4.2 to 4.8 mg/dL. Primary hyperparathyroidism in the outpatient setting and malignancy in hospitalized patients, from either bony metastasis or secretion of parathyroid hormone–related protein, account for most cases of symptomatic hypercalcemia.¹¹ Symptoms of hypercalcemia (see Table 3-6), which vary with the degree of severity, include neurologic impairment, musculoskeletal weakness and pain, renal dysfunction, and GI symptoms of nausea, vomiting, and abdominal pain. Cardiac symptoms can be manifest as hypertension, cardiac arrhythmias, and a worsening of digitalis toxicity. ECG changes in hypercalcemia include shortened QT interval, prolonged PR and QRS intervals, increased QRS voltage, T-wave flattening and widening, and atrioventricular block (which can progress to complete heart block and cardiac arrest).

Hypocalcemia Hypocalcemia is defined as a serum calcium level below 8.5 mEq/L or a decrease in the ionized calcium level below 4.2 mg/dL. The causes of hypocalcemia include pancreatitis, massive soft tissue infections such as necrotizing fasciitis, renal failure, pancreatic and small bowel fistulas, hypoparathyroidism, toxic shock syndrome, abnormalities in magnesium levels, and tumor lysis syndrome. In addition, transient hypocalcemia commonly occurs after removal of a parathyroid adenoma due to atrophy of the remaining glands and avid bone remineralization, and sometimes requires high-dose calcium supplementation.¹² Additionally, malignancies associated with increased osteoblastic activity, such as breast and prostate cancer, can lead to hypocalcemia from increased bone formation.¹³ Calcium precipitation with organic anions is also a cause of hypocalcemia and may occur during hyperphosphatemia from tumor lysis syndrome or rhabdomyolysis. Pancreatitis may sequester calcium via chelation with free fatty acids. Massive blood transfusion with citrate binding is another mechanism.^{14,15} Hypocalcemia rarely results solely from decreased intake, because bone reabsorption can maintain normal levels for prolonged periods.

Asymptomatic hypocalcemia may occur when hypoproteinemia results in a normal ionized calcium level. Conversely, symptoms can develop with a normal serum calcium level during alkalosis, which decreases ionized calcium. In general, neuromuscular and cardiac symptoms do not occur until the ionized fraction falls below 2.5 mg/dL (see Table 3-6). Clinical findings may include paresthesias of the face and extremities, muscle cramps, carpopedal spasm, stridor, tetany, and seizures. Patients will demonstrate hyperreflexia and may exhibit positive Chvostek's sign (spasm resulting from tapping over the facial nerve) and Trousseau's sign (spasm resulting from pressure applied to the nerves and vessels of the upper extremity with a blood pressure cuff). Hypocalcemia may lead to decreased cardiac contractility and heart failure. ECG changes of hypocalcemia include prolonged QT interval, T-wave inversion, heart block, and ventricular fibrillation.

Phosphorus Abnormalities. Phosphorus is the primary intracellular divalent anion and is abundant in metabolically active cells. Phosphorus is involved in energy production during glycolysis and is found in high-energy phosphate products such as adenosine triphosphate. Serum phosphate levels are tightly controlled by renal excretion.

Hyperphosphatemia Hyperphosphatemia can be due to decreased urinary excretion, increased intake, or endogenous mobilization of phosphorus. Most cases of hyperphosphatemia are seen in patients with impaired renal function. Hypoparathyroidism or hyperthyroidism also can decrease urinary excretion of phosphorus and thus lead to hyperphosphatemia. Increased release of endogenous phosphorus can be seen in association with any clinical condition that results in cell destruction, including rhabdomyolysis, tumor lysis syndrome, hemolysis, sepsis, severe hypothermia, and malignant hyperthermia. Excessive phosphate administration from IV hyperalimentation solutions or phosphorus-containing laxatives may also lead to elevated phosphate levels. Most cases of hyperphosphatemia are asymptomatic, but significant prolonged hyperphosphatemia can lead to metastatic deposition of soft tissue calcium-phosphorus complexes.

Hypophosphatemia Hypophosphatemia can be due to a decrease in phosphorus intake, an intracellular shift of phosphorus, or an increase in phosphorus excretion. Decreased GI uptake due to malabsorption or administration of phosphate binders and decreased dietary intake from malnutrition are causes of chronic hypophosphatemia. Most acute cases are due to an intracellular shift of phosphorus in association with respiratory alkalosis, insulin therapy, refeeding syndrome, and hungry bone syndrome. Clinical manifestations of hypophosphatemia usually are absent until levels fall significantly. In general, symptoms are related to adverse effects on the oxygen availability of tissue and to a decrease in high-energy phosphates, and can be manifested as cardiac dysfunction or muscle weakness.

Magnesium Abnormalities. Magnesium is the fourth most common mineral in the body and, like potassium, is found primarily in the intracellular compartments. Approximately one half of the total body content of 2000 mEq is incorporated in bone and is slowly exchangeable. Of the fraction found in the extracellular space, one third is bound to serum albumin. Therefore, the plasma level of magnesium may be a poor indicator of total body stores in the presence of hypoalbuminemia. Magnesium should be replaced until levels are in the upper limit of normal. The normal dietary intake is approximately 20 mEq/d and is excreted in both the feces and urine. The kidneys have a remarkable ability to conserve magnesium, with renal excretion <1 mEq/d during magnesium deficiency.

Hypermagnesemia Hypermagnesemia is rare but can be seen with severe renal insufficiency and parallel changes in potassium excretion. Magnesium-containing antacids and laxatives can produce toxic levels in patients with renal failure. Excess intake in conjunction with total parenteral nutrition (TPN), or rarely massive trauma, thermal injury, and severe acidosis, may be associated with symptomatic hypermagnesemia. Clinical examination (see Table 3-6) may find nausea and vomiting; neuromuscular dysfunction with weakness, lethargy, and hyporeflexia; and impaired cardiac conduction leading to hypotension and arrest. ECG changes are similar to those seen with hyperkalemia and include increased PR interval, widened QRS complex, and elevated T waves.

Hypomagnesemia Magnesium depletion is a common problem in hospitalized patients, particularly in the critically ill.¹⁶ The kidney is primarily responsible for magnesium homeostasis through regulation by calcium/magnesium receptors on the renal tubular cells that respond to serum magnesium concentrations.¹⁷ Hypomagnesemia may result from alterations of intake, renal excretion, and pathologic losses. Poor intake may occur in cases of starvation, alcoholism, prolonged IV fluid therapy, and TPN with inadequate supplementation of magnesium. Losses are seen in cases of increased renal excretion from alcohol abuse, diuretic use, administration of amphotericin B, and primary aldosteronism, as well as GI losses from diarrhea, malabsorption, and acute pancreatitis. The magnesium ion is essential for proper function of many enzyme systems. Depletion is characterized by neuromuscular and central nervous system hyperactivity. Symptoms are similar to those of calcium deficiency, including hyperactive reflexes, muscle tremors, tetany, and positive Chvostek's and Trousseau's signs (see Table 3-6). Severe deficiencies can lead to delirium and seizures. A number of ECG changes also can occur and include prolonged QT and PR intervals, ST-segment depression, flattening or inversion of P waves, torsades de pointes, and arrhythmias. Hypomagnesemia is important not only because of its direct effects on the nervous system but also because it can produce hypocalcemia and lead to persistent hypokalemia. When hypokalemia or hypocalcemia coexists with hypomagnesemia, magnesium should be aggressively replaced to assist in restoring potassium or calcium homeostasis.

Acid-Base Balance

Acid-Base Homeostasis. The pH of body fluids is maintained within a narrow range despite the ability of the kidneys to generate large amounts of HCO_3^- and the normal large acid load produced as a by-product of metabolism. This endogenous acid load is efficiently neutralized by buffer systems and ultimately excreted by the lungs and kidneys.

Important buffers include intracellular proteins and phosphates and the extracellular bicarbonate-carbonic acid system. Compensation for acid-base derangements can be by respiratory mechanisms (for metabolic derangements) or metabolic mechanisms (for respiratory derangements). Changes in ventilation in response to metabolic abnormalities are mediated by hydrogen-sensitive chemoreceptors found in the carotid body and brain stem. Acidosis stimulates the chemoreceptors to increase ventilation, whereas alkalosis decreases the activity of the chemoreceptors and thus decreases ventilation. The kidneys provide compensation for respiratory abnormalities by either increasing or decreasing bicarbonate reabsorption in response to respiratory acidosis or alkalosis, respectively. Unlike the prompt change in ventilation that occurs with metabolic abnormalities, the compensatory response in the kidneys to respiratory abnormalities is delayed. Significant compensation may not begin for 6 hours and then may continue for several days. Because of this delayed compensatory response, respiratory acid-base derangements before renal compensation are classified as acute, whereas those persisting after renal compensation are categorized as chronic.

4► The predicted compensatory changes in response to metabolic or respiratory derangements are listed in Table 3-7.¹⁸ If the predicted change in pH is exceeded, then a mixed acid-base abnormality may be present (Table 3-8).

Metabolic Derangements

Metabolic Acidosis Metabolic acidosis results from an increased intake of acids, an increased generation of acids, or an

Table 3-7

Predicted changes in acid-base disorders

DISORDER	PREDICTED CHANGE
Metabolic	
Metabolic acidosis	$P_{CO_2} = 1.5 \times HCO_3^- + 8$
Metabolic alkalosis	$P_{CO_2} = 0.7 \times HCO_3^- + 21$
Respiratory	
Acute respiratory acidosis	$\Delta pH = (P_{CO_2} - 40) \times 0.008$
Chronic respiratory acidosis	$\Delta pH = (P_{CO_2} - 40) \times 0.003$
Acute respiratory alkalosis	$\Delta pH = (40 - P_{CO_2}) \times 0.008$
Chronic respiratory alkalosis	$\Delta pH = (40 - P_{CO_2}) \times 0.017$

P_{CO_2} = partial pressure of carbon dioxide.

increased loss of bicarbonate (Table 3-9). The body responds by several mechanisms, including producing buffers (extracellular bicarbonate and intracellular buffers from bone and muscle), increasing ventilation (Kussmaul's respirations), and increasing renal reabsorption and generation of bicarbonate. The kidney also will increase secretion of hydrogen and thus increase urinary excretion of NH_4^+ ($H^+ + NH_3^+ = NH_4^+$). Evaluation of a patient with a low serum bicarbonate level and metabolic acidosis includes determination of the anion gap (AG), an index of unmeasured anions.

$$AG = (Na) - (Cl + HCO_3)$$

The normal AG is <12 mmol/L and is due primarily to the albumin effect, so that the estimated AG must be adjusted for albumin (hypoalbuminemia reduces the AG).¹⁹

$$\text{Corrected AG} = \text{actual AG} - [2.5(4.5 - \text{albumin})]$$

Metabolic acidosis with an increased AG occurs either from ingestion of exogenous acid such as from ethylene glycol, salicylates, or methanol, or from increased endogenous acid production of the following:

- β -Hydroxybutyrate and acetoacetate in ketoacidosis
- Lactate in lactic acidosis
- Organic acids in renal insufficiency

A common cause of severe metabolic acidosis in surgical patients is lactic acidosis. In circulatory shock, lactate is produced in the presence of hypoxia from inadequate tissue perfusion. The treatment is to restore perfusion with volume resuscitation rather than to attempt to correct the abnormality with exogenous bicarbonate. With adequate perfusion, the lactic acid is rapidly metabolized by the liver and the pH level returns to normal. In clinical studies of lactic acidosis and ketoacidosis, the administration of bicarbonate has not reduced morbidity or mortality or improved cellular function.²⁰ The overzealous administration of bicarbonate can lead to metabolic alkalosis, which shifts the oxyhemoglobin dissociation curve to the left; this interferes with oxygen unloading at the tissue level and can be associated with arrhythmias that are difficult to treat. An additional disadvantage is that sodium bicarbonate actually can exacerbate intracellular acidosis. Administered bicarbonate can combine with the excess hydrogen ions to form carbonic acid; this is then converted to CO_2 and water, which thus raises the partial pressure of CO_2 (P_{CO_2}). This hypercarbia could compound ventilation abnormalities in patients with underlying acute respiratory distress syndrome. This CO_2 can diffuse into cells, but bicarbonate remains extracellular, which thus worsens intracellular acidosis. Clinically, lactate levels may not be useful in directing resuscitation, although lactate levels may be higher in nonsurvivors of serious injury.²¹

Metabolic acidosis with a normal AG results from exogenous acid administration (HCl or NH_4^+), from loss of bicarbonate due to GI disorders such as diarrhea and fistulas or ureterosigmoidostomy, or from renal losses. In these settings, the bicarbonate loss is accompanied by a gain of chloride; thus, the AG remains unchanged. To determine whether the loss of bicarbonate has a renal cause, the urinary $[NH_4^+]$ can be measured. A low urinary $[NH_4^+]$ in the face of hyperchloremic acidosis would indicate that the kidney is the site of loss, and evaluation for renal tubular acidosis should be undertaken. Proximal renal tubular acidosis results from decreased tubular reabsorption of HCO_3^- , whereas distal renal tubular acidosis results from decreased acid excretion. The carbonic anhydrase

Table 3-8

Respiratory and metabolic components of acid-base disorders

		ACUTE UNCOMPENSATED			CHRONIC (PARTIALLY COMPENSATED)	
TYPE OF ACID-BASE DISORDER	pH	P_{CO_2} (RESPIRATORY COMPONENT)	PLASMA HCO_3^- ^a (METABOLIC COMPONENT)	pH	P_{CO_2} (RESPIRATORY COMPONENT)	PLASMA HCO_3^- ^a (METABOLIC COMPONENT)
Respiratory acidosis	↓↓	↑↑	N	↓	↑↑	↑
Respiratory alkalosis	↑↑	↓↓	N	↑	↓↓	↓
Metabolic acidosis	↓↓	N	↓↓	↓	↓	↓
Metabolic alkalosis	↑↑	N	↑↑	↑	↑?	↑

^aMeasured as standard bicarbonate, whole blood buffer base, CO_2 content, or CO_2 combining power. The base excess value is positive when the standard bicarbonate is above normal and negative when the standard bicarbonate is below normal.

N = normal; P_{CO_2} = partial pressure of carbon dioxide.

Table 3-9

Etiology of metabolic acidosis**Increased Anion Gap Metabolic Acidosis****Exogenous acid ingestion**

- Ethylene glycol
- Salicylate
- Methanol

Endogenous acid production

- Ketoacidosis
- Lactic acidosis
- Renal insufficiency

Normal Anion Gap

- Acid administration (HCl)
- Loss of bicarbonate
- GI losses (diarrhea, fistulas)
- Ureterosigmoidostomy
- Renal tubular acidosis
- Carbonic anhydrase inhibitor

inhibitor acetazolamide also causes bicarbonate loss from the kidneys.

Metabolic Alkalosis Normal acid-base homeostasis prevents metabolic alkalosis from developing unless both an increase in bicarbonate generation and impaired renal excretion of bicarbonate occur (Table 3-10). Metabolic alkalosis results from the loss of fixed acids or the gain of bicarbonate and is worsened by potassium depletion. The majority of patients also will have hypokalemia, because extracellular potassium ions exchange with intracellular hydrogen ions and allow the hydrogen ions to buffer excess HCO_3^- . Hypochloremic and hypokalemic metabolic alkalosis can occur from isolated loss of gastric contents in infants with pyloric stenosis or adults with duodenal ulcer disease. Unlike vomiting associated with an open pylorus,

Table 3-10

Etiology of metabolic alkalosis**Increased bicarbonate generation**

1. Chloride losing (urinary chloride >20 mEq/L)
 - Mineralocorticoid excess
 - Profound potassium depletion
2. Chloride sparing (urinary chloride <20 mEq/L)
 - Loss from gastric secretions (emesis or nasogastric suction)
 - Diuretics
3. Excess administration of alkali
 - Acetate in parenteral nutrition
 - Citrate in blood transfusions
 - Antacids
 - Bicarbonate
 - Milk-alkali syndrome

Impaired bicarbonate excretion

1. Decreased glomerular filtration
2. Increased bicarbonate reabsorption (hypercarbia or potassium depletion)

which involves a loss of gastric as well as pancreatic, biliary, and intestinal secretions, vomiting with an obstructed pylorus results only in the loss of gastric fluid, which is high in chloride and hydrogen, and therefore results in a hypochloremic alkalosis. Initially the urinary bicarbonate level is high in compensation for the alkalosis. Hydrogen ion reabsorption also ensues, with an accompanied potassium ion excretion. In response to the associated volume deficit, aldosterone-mediated sodium reabsorption increases potassium excretion. The resulting hypokalemia leads to the excretion of hydrogen ions in the face of alkalosis, a paradoxical aciduria. Treatment includes replacement of the volume deficit with isotonic saline and then potassium replacement once adequate urine output is achieved.

Respiratory Derangements. Under normal circumstances blood PCO_2 is tightly maintained by alveolar ventilation, controlled by the respiratory centers in the pons and medulla oblongata.

Respiratory Acidosis Respiratory acidosis is associated with the retention of CO_2 secondary to decreased alveolar ventilation. The principal causes are listed in Table 3-11. Because compensation is primarily a renal mechanism, it is a delayed response. Treatment of acute respiratory acidosis is directed at the underlying cause. Measures to ensure adequate ventilation are also initiated. This may entail patient-initiated volume expansion using noninvasive bilevel positive airway pressure or may require endotracheal intubation to increase minute ventilation. In the chronic form of respiratory acidosis, the partial pressure of arterial CO_2 remains elevated and the bicarbonate concentration rises slowly as renal compensation occurs.

Respiratory Alkalosis In the surgical patient, most cases of respiratory alkalosis are acute and secondary to alveolar hyperventilation. Causes include pain, anxiety, and neurologic disorders, including central nervous system injury and assisted ventilation. Drugs such as salicylates, fever, gram-negative bacteremia, thyrotoxicosis, and hypoxemia are other possibilities. Acute hypocapnia can cause an uptake of potassium and phosphate into cells and increased binding of calcium to albumin, leading to symptomatic hypokalemia, hypophosphatemia, and hypocalcemia with subsequent arrhythmias, paresthesias, muscle cramps, and seizures. Treatment should be directed at the underlying cause, but direct treatment of the hyperventilation using controlled ventilation may also be required.

Table 3-11

Etiology of respiratory acidosis: hypoventilation

- Narcotics
- Central nervous system injury
- Pulmonary: significant
 - Secretions
 - Atelectasis
 - Mucus plug
 - Pneumonia
 - Pleural effusion
- Pain from abdominal or thoracic injuries or incisions
- Limited diaphragmatic excursion from intra-abdominal pathology
 - Abdominal distention
 - Abdominal compartment syndrome
 - Ascites

Table 3-12

Electrolyte solutions for parenteral administration

SOLUTION	ELECTROLYTE COMPOSITION (mEq/L)						
	Na	Cl	K	HCO ₃ ⁻	Ca	Mg	mOsm
Extracellular fluid	142	103	4	27	5	3	280–310
Lactated Ringer's	130	109	4	28	3		273
0.9% Sodium chloride	154	154					308
D ₅ 0.45% Sodium chloride	77	77					407
D ₅ W							253
3% Sodium chloride	513	513					1026

D₅ = 5% dextrose; D₅W = 5% dextrose in water.

FLUID AND ELECTROLYTE THERAPY

Parenteral Solutions

A number of commercially available electrolyte solutions are available for parenteral administration. The most commonly used solutions are listed in Table 3-12. The type of fluid administered depends on the patient's volume status and the type of concentration or compositional abnormality present. Both lactated Ringer's solution and normal saline are considered isotonic and are useful in replacing GI losses and correcting extracellular volume deficits. Lactated Ringer's is slightly hypotonic in that it contains 130 mEq of lactate. Lactate is used rather than bicarbonate because it is more stable in IV fluids during storage. It is converted into bicarbonate by the liver after infusion, even in the face of hemorrhagic shock. Evidence has suggested that resuscitation using lactated Ringer's may be deleterious because it activates the inflammatory response and induces apoptosis. The component that has been implicated is the D isomer of lactate, which unlike the L isomer is not a normal intermediary in mammalian metabolism.²² However, subsequent *in vivo* studies showed significantly lower levels of apoptosis in lung and liver tissue after resuscitation with any of the various Ringer's formulations.²³

Sodium chloride is mildly hypertonic, containing 154 mEq of sodium that is balanced by 154 mEq of chloride. The high chloride concentration imposes a significant chloride load on the kidneys and may lead to a hyperchloremic metabolic acidosis. Sodium chloride is an ideal solution, however, for correcting volume deficits associated with hyponatremia, hypochloremia, and metabolic alkalosis.

The less concentrated sodium solutions, such as 0.45% sodium chloride, are useful for replacement of ongoing GI losses as well as for maintenance fluid therapy in the post-operative period. This solution provides sufficient free water for insensible losses and enough sodium to aid the kidneys in adjustment of serum sodium levels. The addition of 5% dextrose (50 g of dextrose per liter) supplies 200 kcal/L, and dextrose is always added to solutions containing <0.45% sodium chloride to maintain osmolality and thus prevent the lysis of red blood cells that may occur with rapid infusion of hypotonic fluids. The addition of potassium is useful once adequate renal function and urine output are established.

Alternative Resuscitative Fluids

A number of alternative solutions for volume expansion and resuscitation are available (Table 3-13).²⁴ Hypertonic saline solutions (3.5% and 5%) are used for correction of severe sodium deficits and are discussed elsewhere in this chapter. Hypertonic saline (7.5%) has been used as a treatment modality in patients with closed head injuries. It has been shown to increase cerebral perfusion and decrease intracranial pressure, thus decreasing brain edema.²⁵ However, there have also been concerns about increased bleeding, because hypertonic saline is an arteriolar vasodilator. A trial of 853 patients receiving hypertonic saline versus hypertonic saline/dextran 70 vs. 0.9% saline as initial resuscitation in the field showed a higher 28-day mortality in both hypertonic saline groups compared to 0.9% saline.²⁶ Colloids also are used in surgical patients, and their effectiveness as volume expanders compared with isotonic crystalloids has long been debated. Due to their molecular weight, they are confined to the intravascular space, and their infusion results in more efficient transient plasma volume expansion. However, under conditions of

Table 3-13

Alternative resuscitative fluids

SOLUTION	MOLECULAR WEIGHT	OSMOLALITY (mOsm/L)	SODIUM (mEq/L)
Hypertonic saline (7.5%)	—	2565	1283
Albumin 5%	70,000	300	130–160
Albumin 25%	70,000	1500	130–160
Dextran 40	40,000	308	154
Dextran 70	70,000	308	154
Hetastarch	450,000	310	154
Hextend	670,000	307	143
Gelofusine	30,000	NA	154

NA = not available.

severe hemorrhagic shock, capillary membrane permeability increases; this permits colloids to enter the interstitial space, which can worsen edema and impair tissue oxygenation. The theory that these high molecular weight agents “plug” capillary leaks, which occur during neutrophil-mediated organ injury, has not been confirmed.^{27,28} Four major types of colloids are available—albumin, dextrans, hetastarch, and gelatins—that are described by their molecular weight and size in Table 3-13. Colloid solutions with smaller particles and lower molecular weights exert a greater oncotic effect but are retained within the circulation for a shorter period of time than larger and higher molecular weight colloids.

Albumin (molecular weight 70,000) is prepared from heat-sterilized pooled human plasma. It is typically available as either a 5% solution (osmolality of 300 mOsm/L) or 25% solution (osmolality of 1500 mOsm/L). Because it is a derivative of blood, it can be associated with allergic reactions. Albumin has been shown to induce renal failure and impair pulmonary function when used for resuscitation in hemorrhagic shock.²⁹

Dextrans are glucose polymers produced by bacteria grown on sucrose media and are available as either 40,000 or 70,000 molecular weight solutions. They lead to initial volume expansion due to their osmotic effect but are associated with alterations in blood viscosity. Thus dextrans are used primarily to lower blood viscosity rather than as volume expanders. Dextrans have been used, in association with hypertonic saline, to help maintain intravascular volume.

Hydroxyethyl starch solutions are another group of alternative plasma expanders and volume replacement solutions. Hetastarches are produced by the hydrolysis of insoluble amylopectin, followed by a varying number of substitutions of hydroxyl groups for carbon groups on the glucose molecules. The molecular weights can range from 1000 to 3,000,000. The high molecular weight hydroxyethyl starch hetastarch, which comes as a 6% solution, is the only hydroxyethyl starch approved for use in the United States. Administration of hetastarch can cause hemostatic derangements related to decreases in von Willebrand's factor and factor VIII:C, and its use has been associated with postoperative bleeding in cardiac and neurosurgery patients.^{30,31} Hetastarch also can induce renal dysfunction in patients with septic shock and was associated with a significant increased risk of mortality and acute kidney injury in the critically ill.^{32,33} Currently, hetastarch has a limited role in massive resuscitation because of the associated coagulopathy and hyperchloremic acidosis (due to its high chloride content). Hextend is a modified, balanced, high molecular weight hydroxyethyl starch that is suspended in a lactate-buffered solution, rather than in saline. A phase III clinical study comparing Hextend to a similar 6% hydroxyethyl starch in patients undergoing major abdominal surgery demonstrated no adverse effects on coagulation with Hextend other than the known effects of hemodilution.³⁴ Hextend has not been tested for use in massive resuscitation, and not all clinical studies show consistent results.³⁵

Gelatins are the fourth group of colloids and are produced from bovine collagen. The two major types are urea-linked gelatin and succinylated gelatin (modified fluid gelatin, Gelo-fusine). Gelo-fusine has been used abroad with mixed results.³⁶ Like many other artificial plasma volume expanders, it has been shown to impair whole blood coagulation time in human volunteers.³⁷

Correction of Life-Threatening Electrolyte Abnormalities

Sodium

Hypernatremia Treatment of hypernatremia usually consists of treatment of the associated water deficit. In hypovolemic patients, volume should be restored with normal saline before the concentration abnormality is addressed. Once adequate volume has been achieved, the water deficit is replaced using a hypotonic fluid such as 5% dextrose, 5% dextrose in ¼ normal saline, or enterally administered water. The formula used to estimate the amount of water required to correct hypernatremia is as follows:

$$\text{Water deficit (L)} = \frac{\text{serum sodium} - 140}{140} \times \text{TBW}$$

Estimate TBW as 50% of lean body mass in men and 40% in women

The rate of fluid administration should be titrated to achieve a decrease in serum sodium concentration of no more than 1 mEq/h and 12 mEq/d for the treatment of acute symptomatic hypernatremia. Even slower correction should be undertaken for chronic hypernatremia (0.7 mEq/h), because overly rapid correction can lead to cerebral edema and herniation. The type of fluid used depends on the severity and ease of correction. Oral or enteral replacement is acceptable in most cases, or IV replacement with half- or quarter-normal saline can be used. Caution also should be exercised when using 5% dextrose in water to avoid overly rapid correction. Frequent neurologic evaluation as well as frequent evaluation of serum sodium levels also should be performed. Hypernatremia is less common than hyponatremia, but has a worse prognosis, and is an independent predictor of mortality in critical illness.³⁸

Hyponatremia Most cases of hyponatremia can be treated by free water restriction and, if severe, the administration of sodium. In patients with normal renal function, symptomatic hyponatremia usually does not occur until the serum sodium level is ≤ 120 mEq/L. If neurologic symptoms are present, 3% normal saline should be used to increase the sodium by no more than 1 mEq/L per hour until the serum sodium level reaches 130 mEq/L or neurologic symptoms are improved. Correction of asymptomatic hyponatremia should increase the sodium level by no more than 0.5 mEq/L per hour to a maximum increase of 12 mEq/L per day, and even more slowly in chronic hyponatremia. The rapid correction of hyponatremia can lead to pontine myelinolysis,³⁹ with seizures, weakness, paresis, akinetic movements, and unresponsiveness, and may result in permanent brain damage and death. Serial magnetic resonance imaging may be necessary to confirm the diagnosis.⁴⁰

Potassium

Hyperkalemia Treatment options for symptomatic hyperkalemia are listed in Table 3-14. The goals of therapy include reducing the total body potassium, shifting potassium from the extracellular to the intracellular space, and protecting the cells from the effects of increased potassium. For all patients, exogenous sources of potassium should be removed, including potassium supplementation in IV fluids and enteral and parenteral solutions. Potassium can be removed from the body using a cation-exchange resin such as Kayexalate that binds potassium in exchange for sodium. It can be administered either

Table 3-14

Treatment of symptomatic hyperkalemia**Potassium removal****Kayexalate**

Oral administration is 15–30 g in 50–100 mL of 20% sorbitol

Rectal administration is 50 g in 200 mL of 20% sorbitol

Dialysis**Shift potassium**

Glucose 1 ampule of D₅₀ and regular insulin 5–10 units IV

Bicarbonate 1 ampule IV

Counteract cardiac effects

Calcium gluconate 5–10 mL of 10% solution

D₅₀ = 50% dextrose.

orally, in alert patients, or rectally. Immediate measures also should include attempts to shift potassium intracellularly with glucose and bicarbonate infusion. Nebulized albuterol (10 to 20 mg) may also be used. Use of glucose alone will cause a rise in insulin secretion, but in the acutely ill, this response may be blunted, and therefore both glucose and insulin may be necessary. Circulatory overload and hypernatremia may result from the administration of Kayexalate and bicarbonate, so care should be exercised when administering these agents to patients with fragile cardiac function. When ECG changes are present, calcium chloride or calcium gluconate (5–10 mL of 10% solution) should be administered immediately to counteract the myocardial effects of hyperkalemia. Calcium infusion should be used cautiously in patients receiving digitalis, because digitalis toxicity may be precipitated. All of the aforementioned measures are temporary, lasting from 1 to approximately 4 hours. Dialysis should be considered in severe hyperkalemia when conservative measures fail.

Hypokalemia Treatment for hypokalemia consists of potassium repletion, the rate of which is determined by the symptoms (Table 3-15). Oral repletion is adequate for mild, asymptomatic hypokalemia. If IV repletion is required, usually no more than 10 mEq/h is advisable in an unmonitored setting. This amount can be increased to 40 mEq/h when accompanied by continuous ECG monitoring, and even more in the case of imminent cardiac arrest from a malignant arrhythmia-associated hypokalemia. Caution should be exercised when oliguria or impaired renal function is coexistent.

Calcium

Hypercalcemia Treatment is required when hypercalcemia is symptomatic, which usually occurs when the serum level exceeds 12 mg/dL. The critical level for serum calcium is 15 mg/dL, when symptoms noted earlier may rapidly progress to death. The initial treatment is aimed at repleting the associated volume deficit and then inducing a brisk diuresis with normal saline. Treatment of hypercalcemia associated with malignancies is discussed later in this chapter.

Hypocalcemia Asymptomatic hypocalcemia can be treated with oral or IV calcium (see Table 3-15). Acute symptomatic hypocalcemia should be treated with IV 10% calcium gluconate to achieve a serum concentration of 7 to 9 mg/dL. Associated deficits in magnesium, potassium, and pH must also be corrected.

Hypocalcemia will be refractory to treatment if coexisting hypomagnesemia is not corrected first. Routine calcium supplementation is no longer recommended in association with massive blood transfusions.⁴¹

Phosphorus

Hyperphosphatemia Phosphate binders such as sucralfate or aluminum-containing antacids can be used to lower serum phosphorus levels. Calcium acetate tablets also are useful when hypocalcemia is simultaneously present. Dialysis usually is reserved for patients with renal failure.

Hypophosphatemia Depending on the level of depletion and tolerance to oral supplementation, a number of enteral and parenteral repletion strategies are effective for the treatment of hypophosphatemia (see Table 3-15).

Magnesium

Hypermagnesemia Treatment for hypermagnesemia consists of measures to eliminate exogenous sources of magnesium, correct concurrent volume deficits, and correct acidosis if present. To manage acute symptoms, calcium chloride (5 to 10 mL) should be administered to immediately antagonize the cardiovascular effects. If elevated levels or symptoms persist, hemodialysis may be necessary.

Hypomagnesemia Correction of magnesium depletion can be oral if asymptomatic and mild. Otherwise, IV repletion is indicated and depends on severity (see Table 3-15) and clinical symptoms. For those with severe deficits (<1.0 mEq/L) or those who are symptomatic, 1 to 2 g of magnesium sulfate may be administered IV over 15 minutes. Under ECG monitoring, it may be given over 2 minutes if necessary to correct torsades de pointes (irregular ventricular rhythm). Caution should be taken when giving large amounts of magnesium, because magnesium toxicity may develop. The simultaneous administration of calcium gluconate will counteract the adverse side effects of a rapidly rising magnesium level and correct hypocalcemia, which is frequently associated with hypomagnesemia.

Preoperative Fluid Therapy

The administration of maintenance fluids should be all that is required in an otherwise healthy individual who may be under orders to receive nothing by mouth for some period before the time of surgery. This does not, however, include replenishment of a pre-existing deficit or ongoing fluid losses. The following is a frequently used formula for calculating the volume of maintenance fluids in the absence of pre-existing abnormalities:

For the first 0–10 kg	Give 100 mL/kg per day
For the next 10–20 kg	Give an additional 50 mL/kg per day
For weight >20 kg	Give an additional 20 mL/kg per day

For example, a 60-kg female would receive a total of 2300 mL of fluid daily: 1000 mL for the first 10 kg of body weight (10 kg × 100 mL/kg per day), 500 mL for the next 20 kg (10 kg × 50 mL/kg per day), and 800 mL for the last 40 kg (40 kg × 20 mL/kg per day).

An alternative approach is to replace the calculated daily water losses in urine, stool, and insensible loss with a hypotonic saline solution rather than water alone, which allows

Table 3-15

Electrolyte replacement therapy protocol

Potassium

Serum potassium level <4.0 mEq/L:

Asymptomatic, tolerating enteral nutrition: KCl 40 mEq per enteral access \times 1 dose

Asymptomatic, not tolerating enteral nutrition: KCl 20 mEq IV q2h \times 2 doses

Symptomatic: KCl 20 mEq IV q1h \times 4 doses

Recheck potassium level 2 h after end of infusion; if <3.5 mEq/L and asymptomatic, replace as per above protocol

Magnesium

Magnesium level 1.0–1.8 mEq/L:

Magnesium sulfate 0.5 mEq/kg in normal saline 250 mL infused IV over 24 h \times 3 d

Recheck magnesium level in 3 d

Magnesium level <1.0 mEq/L:

Magnesium sulfate 1 mEq/kg in normal saline 250 mL infused IV over 24 h \times 1 d, then 0.5 mEq/kg in normal saline 250 mL infused IV over 24 h \times 2 d

Recheck magnesium level in 3 d

If patient has gastric access and needs a bowel regimen:

Milk of magnesia 15 mL (approximately 49 mEq magnesium) q24h per gastric tube; hold for diarrhea

Calcium

Ionized calcium level <4.0 mg/dL:

With gastric access and tolerating enteral nutrition: Calcium carbonate suspension 1250 mg/5 mL q6h per gastric access; recheck ionized calcium level in 3 d

Without gastric access or not tolerating enteral nutrition: Calcium gluconate 2 g IV over 1 h \times 1 dose; recheck ionized calcium level in 3 d

Phosphate

Phosphate level 1.0–2.5 mg/dL:

Tolerating enteral nutrition: Neutra-Phos 2 packets q6h per gastric tube or feeding tube

No enteral nutrition: KPO_4 or NaPO_4 0.15 mmol/kg IV over 6 h \times 1 dose

Recheck phosphate level in 3 d

Phosphate level <1.0 mg/dL:

Tolerating enteral nutrition: KPO_4 or NaPO_4 0.25 mmol/kg over 6 h \times 1 dose

Recheck phosphate level 4 h after end of infusion; if <2.5 mg/dL, begin Neutra-Phos 2 packets q6h

Not tolerating enteral nutrition: KPO_4 or NaPO_4 0.25 mmol/kg (LBW) over 6 h \times 1 dose; recheck phosphate level 4 h after end of infusion; if <2.5 mg/dL, then KPO_4 or NaPO_4 0.15 mmol/kg (LBW) IV over 6 h \times 1 dose

3 mmol KPO_4 = 3 mmol Phos and 4.4 mEq K^+ = 1 mL

3 mmol NaPO_4 = 3 mmol Phos and 4 mEq Na^+ = 1 mL

Neutra-Phos 1 packet = 8 mmol Phos, 7 mEq K^+ , 7 mEq Na^+

Use patient's lean body weight (LBW) in kilograms for all calculations.

Disregard protocol if patient has renal failure, is on dialysis, or has a creatinine clearance <30 mL/min.

the kidney some sodium excess to adjust for concentration. Although there should be no “routine” maintenance fluid orders, both of these methods would yield an appropriate choice of 5% dextrose in 0.45% sodium chloride at 100 mL/h as initial therapy, with potassium added for patients with normal renal function. However, many surgical patients have volume and/or electrolyte abnormalities associated with their surgical disease. Preoperative evaluation of a patient's volume status and pre-existing electrolyte abnormalities is an important part of overall preoperative assessment and care. Volume deficits should be considered in patients who have obvious GI losses, such as through emesis or diarrhea, as well as in patients with poor oral intake secondary to their disease. Less obvious are those fluid losses known as *third-space* or *nonfunctional* ECF losses that occur with GI obstruction, peritoneal or bowel inflammation, ascites, crush injuries, burns, and severe soft tissue infections such as necrotizing fasciitis. The diagnosis of an acute volume

deficit is primarily clinical (see Table 3-2), although the physical signs may vary with the duration of the deficit. Cardiovascular signs of tachycardia and orthostasis predominate with acute volume loss, usually accompanied by oliguria and hemoconcentration. Acute volume deficits should be corrected as much as possible before the time of operation.

Once a volume deficit is diagnosed, prompt fluid replacement should be instituted, usually with an isotonic crystalloid, depending on the measured serum electrolyte values. Patients with cardiovascular signs of volume deficit should receive a bolus of 1 to 2 L of isotonic fluid followed by a continuous infusion. Close monitoring during this period is imperative. Resuscitation should be guided by the reversal of the signs of volume deficit, such as restoration of acceptable values for vital signs, maintenance of adequate urine output ($\frac{1}{2}$ –1 mL/kg per hour in an adult), and correction of base deficit. Patients whose volume deficit is not corrected after this initial volume challenge and

those with impaired renal function and the elderly should be considered for more intensive monitoring in an intensive care unit setting. In these patients, early invasive monitoring of central venous pressure or cardiac output may be necessary.

If symptomatic electrolyte abnormalities accompany volume deficit, the abnormality should be corrected to the point that the acute symptom is relieved before surgical intervention. For correction of severe hyponatremia associated with a volume deficit, an unsafe rapid fall in extracellular osmolality from 5% dextrose infusion is avoided by slowly correcting the hyponatremia with 0.45% saline or even lactated Ringer's solution rather than 5% dextrose alone. This will safely and slowly correct the hyponatremia while also correcting the associated volume deficit.

Intraoperative Fluid Therapy

With the induction of anesthesia, compensatory mechanisms are lost, and hypotension will develop if volume deficits are not appropriately corrected before the time of surgery. Hemodynamic instability during anesthesia is best avoided by correcting known fluid losses, replacing ongoing losses, and providing adequate maintenance fluid therapy preoperatively. In addition to measured blood loss, major open abdominal surgeries are associated with continued extracellular losses in the form of bowel wall edema, peritoneal fluid, and the wound edema during surgery. Large soft tissue wounds, complex fractures with associated soft tissue injury, and burns are all associated with additional third-space losses that must be considered in the operating room. These represent distributional shifts, in that the functional volume of ECF is reduced but fluid is not externally lost from the body. These functional losses have been referred to as *parasitic losses*, *sequestration*, or *third-space edema*, because the lost volume no longer participates in the normal functions of the ECF.

Until the 1960s saline solutions were withheld during surgery. Administered saline was retained and was felt to be an inappropriate challenge to a physiologic response of intraoperative salt intolerance. Basic and clinical research began to change this concept,^{42,43} eventually leading to the current concept that saline administration is necessary to restore the obligate ECF losses noted earlier. Although no accurate formula can predict intraoperative fluid needs, replacement of ECF during surgery often requires 500 to 1000 mL/h of a balanced salt solution to support homeostasis. The addition of albumin or other colloid-containing solutions to intraoperative fluid therapy is not necessary. Manipulation of colloid oncotic forces by albumin infusion during major vascular surgery showed no advantage in supporting cardiac function or avoiding the accumulation of extravascular lung water.⁴⁴

Postoperative Fluid Therapy

Postoperative fluid therapy should be based on the patient's current estimated volume status and projected ongoing fluid losses. Any deficits from either preoperative or intraoperative losses should be corrected, and ongoing requirements should be included along with maintenance fluids. Third-space losses, although difficult to measure, should be included in fluid replacement strategies. In the initial postoperative period, an isotonic solution should be administered. The adequacy of resuscitation should be guided by the restoration of acceptable values for vital signs and urine output and, in more complicated cases, by the correction of base deficit or lactate. If uncertainty

exists, particularly in patients with renal or cardiac dysfunction, a central venous catheter or Swan-Ganz catheter may be inserted to help guide fluid therapy. After the initial 24 to 48 hours, fluids can be changed to 5% dextrose in 0.45% saline in patients unable to tolerate enteral nutrition. If normal renal function and adequate urine output are present, potassium may be added to the IV fluids. Daily fluid orders should begin with assessment of the patient's volume status and assessment of electrolyte abnormalities. There is rarely a need to check electrolyte levels in the first few days of an uncomplicated postoperative course. However, postoperative diuresis may require attention to replacement of urinary potassium loss. All measured losses, including losses through vomiting, nasogastric suctioning, drains, and urine output, as well as insensible losses, are replaced with the appropriate parenteral solutions as previously reviewed.

Special Considerations for the Postoperative Patient

Volume excess is a common disorder in the postoperative period. The administration of isotonic fluids in excess of actual needs may result in excess volume expansion. This may be due to the overestimation of third-space losses or to ongoing GI losses that are difficult to measure accurately. The earliest sign of volume overload is weight gain. The average postoperative patient who is not receiving nutritional support should lose approximately 0.25 to 0.5 lb/d (0.11 to 0.23 kg/d) from catabolism. Additional signs of volume excess may also be present as listed in Table 3-2. Peripheral edema may not necessarily be associated with intravascular volume overload, because overexpansion of total ECF may exist in association with a deficit in the circulating plasma volume.

Volume deficits also can be encountered in surgical patients if preoperative losses were not completely corrected, intraoperative losses were underestimated, or postoperative losses were greater than appreciated. The clinical manifestations are described in Table 3-2 and include tachycardia, orthostasis, and oliguria. Hemoconcentration also may be present. Treatment will depend on the amount and composition of fluid lost. In most cases of volume depletion, replacement with an isotonic fluid will be sufficient while alterations in concentration and composition are being evaluated.

ELECTROLYTE ABNORMALITIES IN SPECIFIC SURGICAL PATIENTS

Neurologic Patients

Syndrome of Inappropriate Secretion of Antidiuretic Hormone. The syndrome of inappropriate secretion of antidiuretic hormone (SIADH) can occur after head injury or surgery to the central nervous system, but it also is seen in association with administration of drugs such as morphine, nonsteroidals, and oxytocin, and in a number of pulmonary and endocrine diseases, including hypothyroidism and glucocorticoid deficiency. Additionally, it can be seen in association with a number of malignancies, most often small cell cancer of the lung but also pancreatic carcinoma, thymoma, and Hodgkin's disease.⁴⁵ SIADH should be considered in patients who are euvolemic and hyponatremic with elevated urine sodium levels and urine osmolality. ADH secretion is considered inappropriate when it is not in response to osmotic or volume-related conditions. Correction of the underlying problem should be attempted

when possible. In most cases, restriction of free water will improve the hyponatremia. The goal is to achieve net water balance while avoiding volume depletion that may compromise renal function. Furosemide also can be used to induce free water loss. If hyponatremia persists after fluid restriction, the addition of isotonic or hypertonic fluids may be effective. The administration of isotonic saline may sometimes worsen the problem if the urinary sodium concentration is higher than the infused sodium concentration. The use of loop diuretics may be helpful in this situation by preventing further urine concentration. In chronic SIADH, when long-term fluid restriction is difficult to maintain or is ineffective, demeclocycline and lithium can be used to induce free water loss.

Diabetes Insipidus. Diabetes insipidus (DI) is a disorder of ADH stimulation and is manifested by dilute urine in the case of hypernatremia. Central DI results from a defect in ADH secretion, and nephrogenic DI results from a defect in end-organ responsiveness to ADH. Central DI is frequently seen in association with pituitary surgery, closed head injury, and anoxic encephalopathy.⁴⁶ Nephrogenic DI occurs in association with hypokalemia, administration of radiocontrast dye, and use of certain drugs such as aminoglycosides and amphotericin B. In patients tolerating oral intake, volume status usually is normal because thirst stimulates increased intake. However, volume depletion can occur rapidly in patients incapable of oral intake. The diagnosis can be confirmed by documenting a paradoxical increase in urine osmolality in response to a period of water deprivation. In mild cases, free water replacement may be adequate therapy. In more severe cases, vasopressin can be added. The usual dosage of vasopressin is 5 U subcutaneously every 6 to 8 hours. However, serum electrolytes and osmolality should be monitored to avoid excess vasopressin administration with resulting iatrogenic SIADH.

Cerebral Salt Wasting. Cerebral salt wasting is a diagnosis of exclusion that occurs in patients with a cerebral lesion and renal wasting of sodium and chloride with no other identifiable cause.⁴⁷ Natriuresis in a patient with a contracted extracellular volume should prompt the possible diagnosis of cerebral salt wasting. Hyponatremia is frequently observed but is nonspecific and occurs as a secondary event, which differentiates it from SIADH.

Malnourished Patients: Refeeding Syndrome

Refeeding syndrome is a potentially lethal condition that can occur with rapid and excessive feeding of patients with severe underlying malnutrition due to starvation, alcoholism, delayed nutritional support, anorexia nervosa, or massive weight loss in obese patients.⁴⁸ With refeeding, a shift in metabolism from fat to carbohydrate substrate stimulates insulin release, which results in the cellular uptake of electrolytes, particularly phosphate, magnesium, potassium, and calcium. However, severe hyperglycemia may result from blunted basal insulin secretion. The refeeding syndrome can be associated with enteral or parenteral refeeding, and symptoms from electrolyte abnormalities include cardiac arrhythmias, confusion, respiratory failure, and even death. To prevent the development of refeeding syndrome, underlying electrolyte and volume deficits should be corrected. Additionally, thiamine should be administered before the initiation of feeding. Caloric repletion should be instituted slowly and should gradually increase over the first week.⁴⁹ Vital signs, fluid balance, and electrolytes should be closely monitored and any deficits corrected as they evolve.

Acute Renal Failure Patients

A number of fluid and electrolyte abnormalities are specific to patients with acute renal failure. With the onset of renal failure, an accurate assessment of volume status must be made. If prerenal azotemia is present, prompt correction of the underlying volume deficit is mandatory. Once acute tubular necrosis is established, measures should be taken to restrict daily fluid intake to match urine output and insensible and GI losses. Oliguric renal failure requires close monitoring of serum potassium levels. Measures to correct hyperkalemia as reviewed in Table 3-14 should be instituted early, including consideration of early hemodialysis. Hyponatremia is common in established renal failure as a result of the breakdown of proteins, carbohydrates, and fats, as well the administration of free water. Dialysis may be required for severe hyponatremia. Hypocalcemia, hypermagnesemia, and hyperphosphatemia also are associated with acute renal failure. Hypocalcemia should be verified by measuring ionized calcium, because many patients also are hypoalbuminemic. Phosphate binders can be used to control hyperphosphatemia, but dialysis may be required in more severe cases. Metabolic acidosis is commonly seen with renal failure, as the kidneys lose their ability to clear acid by-products. Bicarbonate can be useful, but dialysis often is needed. Although dialysis may be either intermittent or continuous, renal recovery may be improved by continuous renal replacement.⁵⁰

Cancer Patients

Fluid and electrolyte abnormalities are common in patients with cancer. The causes may be common to all patient populations or may be specific to cancer patients and their treatment.⁵¹ Hyponatremia is frequently hypovolemic due to renal loss of sodium caused by diuretics or salt-wasting nephropathy as seen with some chemotherapeutic agents such as cisplatin. Cerebral salt wasting also can occur in patients with intracerebral lesions. Normovolemic hyponatremia may occur in association with SIADH from cervical cancer, lymphoma, and leukemia, or from certain chemotherapeutic agents. Hypernatremia in cancer patients most often is due to poor oral intake or GI volume losses, which are common side effects of chemotherapy. Central DI also can lead to hypernatremia in patients with central nervous system lesions.

Hypokalemia can develop from GI losses associated with diarrhea caused by radiation enteritis or chemotherapy, or from tumors such as villous adenomas of the colon. Tumor lysis syndrome can precipitate severe hyperkalemia from massive tumor cell destruction.

Hypocalcemia can be seen after removal of a thyroid or parathyroid tumor or after a central neck dissection, which can damage the parathyroid glands. Hungry bone syndrome produces acute and profound hypocalcemia after parathyroid surgery for secondary or tertiary hyperparathyroidism because calcium is rapidly taken up by bones. Prostate and breast cancer can result in increased osteoblastic activity, which decreases serum calcium by increasing bone formation. Acute hypocalcemia also can occur with hyperphosphatemia, because phosphorus complexes with calcium. Hypomagnesemia is a side effect of ifosfamide and cisplatin therapy. Hypophosphatemia can be seen in hyperparathyroidism, due to decreased phosphorus reabsorption, and in oncogenic osteomalacia, which increases the urinary excretion of phosphorus. Other causes of hypophosphatemia in cancer patients include renal tubular dysfunction from multiple myeloma, Bence Jones proteins, and certain chemotherapeutic agents.

Acute hypophosphatemia can occur as rapidly proliferating malignant cells take up phosphorus in acute leukemia. Tumor lysis syndrome or the use of bisphosphonates to treat hypercalcemia also can result in hyperphosphatemia.

Malignancy is the most common cause of hypercalcemia in hospitalized patients and is due to increased bone resorption or decreased renal excretion. Bone destruction occurs from bony metastasis as seen in breast or renal cell cancer but also can occur in multiple myeloma. With Hodgkin's and non-Hodgkin's lymphoma, hypercalcemia results from increased calcitriol formation, which increases both absorption of calcium from the GI tract and mobilization from bone. Humoral hypercalcemia of malignancy is a common cause of hypercalcemia in cancer patients. As in primary hyperparathyroidism, a parathyroid-related protein is secreted that binds to parathyroid receptors, stimulating calcium resorption from bone and decreasing renal excretion of calcium. The treatment of hypercalcemia of malignancy should begin with saline volume expansion, which will decrease renal reabsorption of calcium as the associated volume deficit is corrected. Once an adequate volume status has been achieved, a loop diuretic may be added. Unfortunately, these measures are only temporary, and additional treatment is often necessary. A variety of drugs are available with varying times of onset, durations of action, and side effects.⁵² The bisphosphonates etidronate and pamidronate inhibit bone resorption and osteoclastic activity. They have a slow onset of action, but effects can last for 2 weeks. Calcitonin also is effective, inhibiting bone resorption and increasing renal excretion of calcium. It acts quickly, within 2 to 4 hours, but its use is limited by the development of tachyphylaxis. Corticosteroids may decrease tachyphylaxis in response to calcitonin and can be used alone to treat hypercalcemia. Gallium nitrates are potent inhibitors of bone resorption. They display a long duration of action but can cause nephrotoxicity. Mithramycin is an antibiotic that blocks osteoclastic activity, but it can be associated with liver, renal, and hematologic abnormalities, which limits its use to the treatment of Paget's disease of bone. For patients with severe, refractory hypercalcemia who are unable to tolerate volume expansion due to pulmonary edema or congestive heart failure, dialysis is an option.

Tumor lysis syndrome results when the release of intracellular metabolites overwhelms the kidneys' excretory capacity. This rapid release of uric acid, potassium, and phosphorus can result in marked hyperuricemia, hyperkalemia, hyperphosphatemia, and hypocalcemia, and acute renal failure. It is typically seen with poorly differentiated lymphomas and leukemias but also can occur with a number of solid tumor malignancies. Tumor lysis syndrome most commonly develops during treatment with chemotherapy or radiotherapy. Once it develops, volume expansion should be undertaken and any associated electrolyte abnormalities corrected. In this setting, hypocalcemia should not be treated unless it is symptomatic to avoid metastatic calcifications. Dialysis may be required for management of impaired renal function or correction of electrolyte abnormalities.

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chapter

Hemostasis, Surgical Bleeding, and Transfusion

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BIOLOGY OF HEMOSTASIS

Hemostasis is a complex process whose function is to limit blood loss from an injured vessel. Four major physiologic events participate in the hemostatic process: vascular constriction, platelet plug formation, fibrin formation, and fibrinolysis. Although each tends to be activated in order, the four processes are interrelated so that there is a continuum and multiple reinforcements. The process is shown schematically in Fig. 4-1.

Vascular Constriction

Vascular constriction is the initial response to vessel injury. It is more pronounced in vessels with medial smooth muscles and is dependent on local contraction of smooth muscle. Vasoconstriction is subsequently linked to platelet plug formation. Thromboxane A₂ (TXA₂) is produced locally at the site of injury via the release of arachidonic acid from platelet membranes and is a potent constrictor of smooth muscle. Similarly, endothelin synthesized by injured endothelium and serotonin (5-hydroxytryptamine [5-HT]) released during platelet aggregation are potent vasoconstrictors. Lastly, bradykinin and fibrinopeptides, which are involved in the coagulation schema, are also capable of contracting vascular smooth muscle.

The extent of vasoconstriction varies with the degree of vessel injury. A small artery with a lateral incision may remain open due to physical forces, whereas a similarly sized vessel that is completely transected may contract to the extent that bleeding ceases spontaneously.

Platelet Function

Platelets are anucleate fragments of megakaryocytes. The normal circulating number of platelets ranges between 150,000 and 400,000/ μ L. Up to 30% of circulating platelets may be sequestered in the spleen. If not consumed in a clotting reaction,

platelets are normally removed by the spleen and have an average life span of 7 to 10 days.

Platelets play an integral role in hemostasis by forming a hemostatic plug and by contributing to thrombin formation (Fig. 4-2). Platelets do not normally adhere to each other or to the vessel wall but can form a plug that aids in cessation of bleeding when vascular disruption occurs. Injury to the intimal layer in the vascular wall exposes subendothelial collagen to which platelets adhere. This process requires von Willebrand factor (vWF), a protein in the subendothelium that is lacking in patients with von Willebrand's disease. vWF binds to glycoprotein (GP) I/IX/V on the platelet membrane. Following adhesion, platelets initiate a release reaction that recruits other platelets from the circulating blood to seal the disrupted vessel. Up to this point, this process is known as primary hemostasis. Platelet aggregation is reversible and is not associated with secretion. Additionally, heparin does not interfere with this reaction, and thus, hemostasis can occur in the heparinized patient. Adenosine diphosphate (ADP) and serotonin are the principal mediators in platelet aggregation.

Arachidonic acid released from the platelet membranes is converted by cyclooxygenase to prostaglandin G₂ (PGG₂) and then to prostaglandin H₂ (PGH₂), which, in turn, is converted to TXA₂. TXA₂ has potent vasoconstriction and platelet aggregation effects. Arachidonic acid may also be shuttled to adjacent endothelial cells and converted to prostacyclin (PGI₂), which is a vasodilator and acts to inhibit platelet aggregation. Platelet cyclooxygenase is irreversibly inhibited by aspirin and reversibly blocked by nonsteroidal anti-inflammatory agents, but is not affected by cyclooxygenase-2 (COX-2) inhibitors.

In the second wave of platelet aggregation, a release reaction occurs in which several substances including ADP, Ca²⁺, serotonin, TXA₂, and α -granule proteins are discharged. Fibrinogen is a required cofactor for this process, acting as a bridge for

Key Points

- 1▶ The life span of platelets ranges from 7 to 10 days. Drugs that interfere with platelet function include aspirin, clopidogrel, prasugrel, dipyridamole, and the glycoprotein IIb/IIIa (GP IIb/IIIa) inhibitors. Approximately 5 to 7 days should pass from the time the drug is stopped until an elective procedure is performed.
- 2▶ The acute coagulopathy of trauma results from a combination of activation of protein C and hyperfibrinolysis. It is distinct from disseminated intravascular coagulation, is present on arrival to the emergency department, and is associated with an increase in mortality.
- 3▶ Newer anticoagulants like dabigatran and rivaroxaban have no readily available method of detection of the degree of anticoagulation and may not be readily reversible.
- 4▶ Therapeutic anticoagulation preoperatively and postoperatively is becoming increasingly more common. The patient's risk of intraoperative and postoperative bleeding should guide the need for reversal of anticoagulation therapy preoperatively and the timing of its reinstatement postoperatively.
- 5▶ Damage control resuscitation has three basic components: permissive hypotension, minimizing crystalloid-based resuscitation, and the administration of predefined blood products.
- 6▶ The need for massive transfusion should be anticipated, and guidelines should be in place to provide early and increased amounts of red blood cells, plasma, and platelets.

the GP IIb/IIIa receptor on the activated platelets. The release reaction results in compaction of the platelets into a plug, a process that is no longer reversible. Thrombospondin, another protein secreted by the α -granule, stabilizes fibrinogen binding to the activated platelet surface and strengthens the platelet-platelet interactions. Platelet factor 4 (PF4) and α -thromboglobulin are also secreted during the release reaction. PF4 is a potent heparin antagonist. The second wave of platelet aggregation is inhibited by aspirin and nonsteroidal anti-inflammatory drugs, by cyclic adenosine monophosphate (cAMP), and by nitric oxide. As a consequence of the release reaction, alterations occur in the phospholipids of the platelet membrane that allow calcium and clotting factors to bind to the platelet surface, forming enzymatically active complexes. The altered lipoprotein surface (sometimes referred to as platelet factor 3) catalyzes reactions that are involved in the conversion of prothrombin (factor II) to

thrombin (factor IIa) by activated factor X (Xa) in the presence of factor V and calcium, and it is involved in the reaction by which activated factor IX (IXa), factor VIII, and calcium activate factor X. Platelets may also play a role in the initial activation of factors XI and XII.

Coagulation

Hemostasis involves a complex interplay and combination of interactions between platelets, the endothelium, and multiple circulating or membrane-bound coagulation factors. While a bit simplistic and not reflective of the depth or complexity of these interactions, the coagulation cascade has traditionally been depicted as two possible pathways converging into a single common pathway (Fig. 4-3). While this pathway reflects the basic process and sequences that lead to the formation of a clot, the numerous feedback loops, endothelial interplay, and platelet

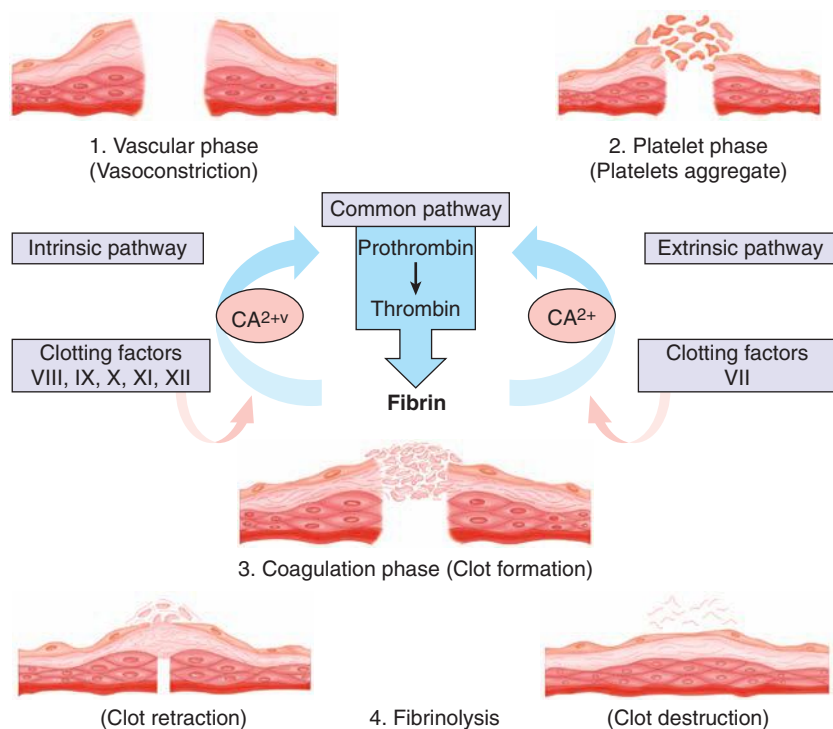


Figure 4-1. Biology of hemostasis. The four physiologic processes that interrelate to limit blood loss from an injured vessel are illustrated and include vascular constriction, platelet plug formation, fibrin clot formation, and fibrinolysis.

In seeking to balance profound bleeding with overwhelming clot burden, several related processes exist to prevent propagation of the clot beyond the site of injury.¹ First, feedback inhibition on the coagulation cascade deactivates the enzyme complexes leading to thrombin formation. Thrombomodulin (TM) presented by the endothelium serves as a “thrombin sink” by forming a complex with thrombin, rendering it no longer available to cleave fibrinogen. This then activates protein C (APC) and reduces further thrombin generation by inhibiting factors V and VIII. Second, tissue plasminogen activator (tPA) is released from the endothelium following injury, cleaving plasminogen to initiate fibrinolysis. APC then consumes plasminogen activator inhibitor-1 (PAI-1), leading to increased tPA activity and fibrinolysis. Building on the anticoagulant response to inhibit thrombin formation, tissue factor pathway inhibitor (TFPI) is released, blocking the TF-VIIa complex and reducing the production of factors Xa and IXa. Antithrombin III (AT-III) then neutralizes all of the procoagulant serine proteases and also inhibits the TF-VIIa complex. The most potent mechanism of thrombin inhibition involves the APC system. APC forms a complex with its cofactor, protein S, on a phospholipid surface. This complex then cleaves factors Va and VIIIa so they are no longer able to participate in the formation of TF-VIIa or prothrombinase complexes. This is of interest clinically in the form of a genetic mutation, called factor V Leiden. In this setting, factor V is resistant to cleavage by APC, thereby remaining active as a procoagulant. Patients with factor V Leiden are predisposed to venous thromboembolic events.

Degradation of fibrin clot is accomplished by plasmin, a serine protease derived from the proenzyme plasminogen. Plasmin formation occurs as a result of one of several plasminogen activators. tPA is made by the endothelium and other cells of the vascular wall and is the main circulating form of this family of enzymes. tPA is selective for fibrin-bound plasminogen so that endogenous fibrinolytic activity occurs predominately at the site of clot formation. The other major plasminogen activator, urokinase plasminogen activator (uPA), also produced by endothelial cells as well as by urothelium, is not selective for fibrin-bound plasminogen. Of note, the thrombin-TM complex activates TAFI, leading to a mixed effect on clot stability. In addition to inhibiting fibrinolysis directly, removal of the terminal lysine on the fibrin molecule by TAFI renders the clot more susceptible to lysis by plasmin.

Fibrinolysis

Fibrin clot breakdown (lysis) allows restoration of blood flow during the healing process following injury and begins at the same time clot formation is initiated. Fibrin polymers are degraded by plasmin, a serine protease derived from the proenzyme plasminogen. Plasminogen is converted to plasmin by one of several plasminogen activators, including tPA. Plasmin then degrades the fibrin mesh at various places, leading to the production of circulating fragments, termed fibrin degradation products (FDPs), cleared by other proteases or by the kidney and liver (Fig. 4-4). Fibrinolysis is directed by circulating kinases, tissue activators, and kallikrein present in vascular endothelium. tPA is synthesized by endothelial cells and released by the cells on thrombin stimulation. Bradykinin, a potent endothelial-dependent vasodilator, is cleaved from high molecular weight kininogen by kallikrein and enhances the release of tPA. Both tPA and plasminogen bind to fibrin as it forms, and this trimolecular complex cleaves fibrin very efficiently. After plasmin is generated, however, it cleaves fibrin somewhat less efficiently.

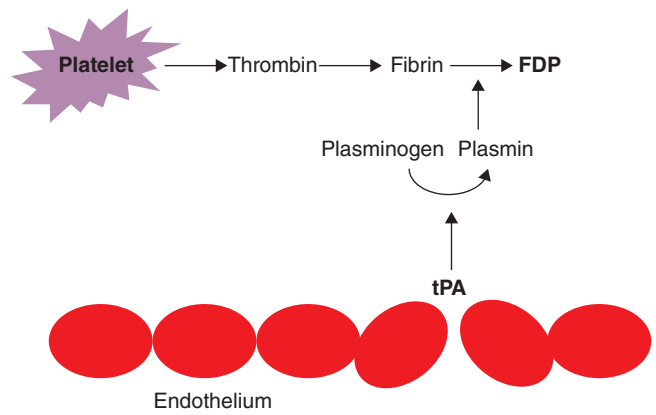


Figure 4-4. Formation of fibrin degradation products (FDPs). tPA = tissue plasminogen activator.

As with clot formation, fibrinolysis is also kept in check through several robust mechanisms. tPA activates plasminogen more efficiently when it is bound to fibrin, so that plasmin is formed selectively on the clot. Plasmin is inhibited by α_2 -antiplasmin, a protein that is cross-linked to fibrin by factor XIII, which helps to ensure that clot lysis does not occur too quickly. Any circulating plasmin is also inhibited by α_2 -antiplasmin and circulating tPA or urokinase. Clot lysis yields FDPs including E-nodes and D-dimers. These smaller fragments interfere with normal platelet aggregation, and the larger fragments may be incorporated into the clot in lieu of normal fibrin monomers. This may result in an unstable clot as seen in cases of severe coagulopathy such as hyperfibrinolysis associated with trauma-induced coagulopathy or disseminated intravascular coagulopathy. The presence of D-dimers in the circulation may serve as a marker of thrombosis or other conditions in which a significant activation of the fibrinolytic system is present. Another inhibitor of the fibrinolytic system is TAFI, which removes lysine residues from fibrin that are essential for binding plasminogen.

CONGENITAL FACTOR DEFICIENCIES

Coagulation Factor Deficiencies

Inherited deficiencies of all of the coagulation factors are seen. However, the three most frequent are factor VIII deficiency (hemophilia A and von Willebrand's disease), factor IX deficiency (hemophilia B or Christmas disease), and factor XI deficiency. Hemophilia A and hemophilia B are inherited as sex-linked recessive disorders with males being affected almost exclusively. The clinical severity of hemophilia A and hemophilia B depends on the measurable level of factor VIII or factor IX in the patient's plasma. Plasma factor levels less than 1% of normal are considered severe disease, factor levels between 1% and 5% moderately severe disease, and levels between 5% and 30% mild disease. Patients with severe hemophilia have spontaneous bleeds, frequently into joints, leading to crippling arthropathies. Intracranial bleeding, intramuscular hematomas, retroperitoneal hematomas, and gastrointestinal, genitourinary, and retropharyngeal bleeding are added clinical sequelae seen with severe disease. Patients with moderately severe hemophilia have less spontaneous bleeding but are likely to bleed severely after trauma or surgery. Mild hemophiliacs do not bleed spontaneously and have only minor bleeding after major trauma or surgery. Since platelet function is normal in hemophiliacs, patients may not bleed immediately after an injury or minor surgery as

they have a normal response with platelet activation and formation of a platelet plug. At times, the diagnosis of hemophilia is not made in these patients until after their first minor procedure (e.g., tooth extraction or tonsillectomy).

Patients with hemophilia A or B are treated with factor VIII or factor IX concentrate, respectively. Recombinant factor VIII is strongly recommended for patients not treated previously and is generally recommended for patients who are both human immunodeficiency virus (HIV) and hepatitis C virus (HCV) seronegative. For factor IX replacement, the preferred products are recombinant or high-purity factor IX. In general, activity levels should be restored to 30% to 40% for mild hemorrhage, 50% for severe bleeding, and 80% to 100% for life-threatening bleeding. Up to 20% of hemophiliacs with factor VIII deficiency develop inhibitors that can neutralize FVIII. For patients with low titers, inhibitors can be overcome with higher doses of factor VIII. For patients with high titer inhibitors, alternate treatments should be used and may include porcine factor VIII, prothrombin complex concentrates, activated prothrombin complex concentrates, or recombinant factor VIIa. For patients undergoing elective surgical procedures, a multidisciplinary approach with preoperative planning and replacement is recommended.²

von Willebrand's Disease. von Willebrand's disease (vWD), the most common congenital bleeding disorder, is characterized by a quantitative or qualitative defect in vWF, a large glycoprotein responsible for carrying factor VIII and platelet adhesion. The latter is important for normal platelet adhesion to exposed subendothelium and for aggregation under high shear conditions. Patients with vWD have bleeding that is characteristic of platelet disorders such as easy bruising and mucosal bleeding. Menorrhagia is common in women. vWD is classified into three types. Type I is a partial quantitative deficiency, type II is a qualitative defect, and type III is total deficiency. For bleeding, type I patients usually respond well to desmopressin (DDAVP). Type II patients may respond, depending on the particular defect. Type III patients are usually unresponsive. These patients may require vWF concentrates.³

Factor XI Deficiency. Factor XI deficiency, an autosomal recessive inherited condition sometimes referred to as hemophilia C, is more prevalent in the Ashkenazi Jewish population but found in all races. Spontaneous bleeding is rare, but bleeding may occur after surgery, trauma, or invasive procedures. Treatment of patients with factor XI deficiency who present with bleeding or in whom surgery is planned and who are known to have bled previously is with fresh frozen plasma (FFP). Each milliliter of plasma contains 1 unit of factor XI activity, so the volume needed depends on the patient's baseline level, the desired level, and the plasma volume. Antifibrinolytics may be useful in patients with menorrhagia. Factor VIIa is recommended for patients with anti-factor XI antibodies, although thrombosis has been reported.⁴ There has been renewed interest in factor XI inhibitors as antithrombotic agents, because patients with factor XI deficiency generally have only minimal bleeding risk unless a severe deficiency is present and seem to be protected from thrombosis.⁵

Deficiency of Factors II (Prothrombin), V, and X. Inherited deficiencies of factors II, V, and X are rare. These deficiencies are inherited as autosomal recessive. Significant bleeding in homozygotes with less than 1% of normal activity is encountered. Bleeding with any of these deficiencies is treated with FFP. Similar to factor XI, FFP contains one unit of activity

of each per milliliter. However, factor V activity is decreased because of its inherent instability. The half-life of prothrombin (factor II) is long (approximately 72 hours), and only about 25% of a normal level is needed for hemostasis. Prothrombin complex concentrates can be used to treat deficiencies of prothrombin or factor X. Daily infusions of FFP are used to treat bleeding in factor V deficiency, with a goal of 20% to 25% activity. Factor V deficiency may be coinherited with factor VIII deficiency. Treatment of bleeding in individuals with the combined deficiency requires factor VIII concentrate and FFP. Some patients with factor V deficiency are also lacking the factor V normally present in platelets and may need platelet transfusions as well as FFP.

Factor VII Deficiency. Inherited factor VII deficiency is a rare autosomal recessive disorder. Clinical bleeding can vary widely and does not always correlate with the level of FVII coagulant activity in plasma. Bleeding is uncommon unless the level is less than 3%. The most common bleeding manifestations involve easy bruising and mucosal bleeding, particularly epistaxis or oral mucosal bleeding. Postoperative bleeding is also common, reported in 30% of surgical procedures.⁶ Treatment is with FFP or recombinant factor VIIa. The half-life of recombinant factor VIIa is only approximately 2 hours, but excellent hemostasis can be achieved with frequent infusions. The half-life of factor VII in FFP is up to 4 hours.

Factor XIII Deficiency. Congenital factor XIII (FXIII) deficiency, originally recognized by Duckert in 1960, is a rare autosomal recessive disease usually associated with a severe bleeding diathesis.⁷ The male-to-female ratio is 1:1. Although acquired FXIII deficiency has been described in association with hepatic failure, inflammatory bowel disease, and myeloid leukemia, the only significant association with bleeding in children is the inherited deficiency.⁸ Bleeding is typically delayed because clots form normally but are susceptible to fibrinolysis. Umbilical stump bleeding is characteristic, and there is a high risk of intracranial bleeding. Spontaneous abortion is usual in women with factor XIII deficiency unless they receive replacement therapy. Replacement can be accomplished with FFP, cryoprecipitate, or a factor XIII concentrate. Levels of 1% to 2% are usually adequate for hemostasis.

Platelet Functional Defects

Inherited platelet functional defects include abnormalities of platelet surface proteins, abnormalities of platelet granules, and enzyme defects. The major surface protein abnormalities are thrombasthenia and Bernard-Soulier syndrome. Thrombasthenia, or Glanzmann thrombasthenia, is a rare genetic platelet disorder, inherited in an autosomal recessive pattern, in which the platelet glycoprotein IIb/IIIa (GP IIb/IIIa) complex is either lacking or present but dysfunctional. This defect leads to faulty platelet aggregation and subsequent bleeding. The disorder was first described by Dr. Eduard Glanzmann in 1918.⁹ Bleeding in thrombasthenic patients must be treated with platelet transfusions. The Bernard-Soulier syndrome is caused by a defect in the GP Ib/IX/V receptor for vWF, which is necessary for platelet adhesion to the subendothelium. Transfusion of normal platelets is required for bleeding in these patients.

The most common intrinsic platelet defect is storage pool disease. It involves loss of dense granules (storage sites for ADP, adenosine triphosphate [ATP], Ca^{2+} , and inorganic phosphate) and α -granules. Dense granule deficiency is the most prevalent of these. It may be an isolated defect or occur with

partial albinism in the Hermansky-Pudlak syndrome. Bleeding is variable, depending on the severity of the granule defect. Bleeding is caused by the decreased release of ADP from these platelets. A few patients have been reported who have decreased numbers of both dense and α -granules. They have a more severe bleeding disorder. Patients with mild bleeding as a consequence of a form of storage pool disease can be treated with DDAVP. It is likely that the high levels of vWF in the plasma after DDAVP somehow compensate for the intrinsic platelet defect. With more severe bleeding, platelet transfusion is required.

ACQUIRED HEMOSTATIC DEFECTS

Platelet Abnormalities

Acquired abnormalities of platelets are much more common than acquired defects and may be quantitative or qualitative, although some patients have both types of defects. Quantitative defects may be a result of failure of production, shortened survival, or sequestration. Failure of production is generally a result of bone marrow disorders such as leukemia, myelodysplastic syndrome, severe vitamin B₁₂ or folate deficiency, chemotherapeutic drugs, radiation, acute ethanol intoxication, or viral infection. If a quantitative abnormality exists and treatment is indicated either due to symptoms or the need for an invasive procedure, platelet transfusion is utilized. The etiologies of both qualitative and quantitative defects are reviewed in Table 4-1.

Table 4-1

Etiology of platelet disorders

- A. Quantitative Disorders
 - 1. Failure of production: related to impairment in bone marrow function
 - a. Leukemia
 - b. Myeloproliferative disorders
 - c. B₁₂ or folate deficiencies
 - d. Chemotherapy or radiation therapy
 - e. Acute alcohol intoxication
 - f. Viral infections
 - 2. Decreased survival
 - a. Immune-mediated
 - 1) Idiopathic thrombocytopenia (ITP)
 - 2) Heparin-induced thrombocytopenia
 - 3) Autoimmune disorders or B-cell malignancies
 - 4) Secondary thrombocytopenia
 - b. Disseminated intravascular coagulation (DIC)
 - c. Related to platelet thrombi
 - 1) Thrombocytopenic purpura (TTP)
 - 2) Hemolytic uremic syndrome (HS)
 - 3. Sequestration
 - a. Portal hypertension
 - b. Sarcoid
 - c. Lymphoma
 - d. Gaucher's Disease
- B. Qualitative Disorders
 - 1. Massive transfusion
 - 2. Therapeutic platelet inhibitors
 - 3. Disease states
 - a. Myeloproliferative disorders
 - b. Monoclonal gammopathies
 - c. Liver disease

Quantitative Defects. Shortened platelet survival is seen in immune thrombocytopenia, disseminated intravascular coagulation, or disorders characterized by platelet thrombi such as thrombotic thrombocytopenic purpura and hemolytic uremic syndrome. Immune thrombocytopenia may be idiopathic or associated with other autoimmune disorders or low-grade B-cell malignancies, and it may also be secondary to viral infections (including HIV) or drugs. Secondary immune thrombocytopenia often presents with a very low platelet count, petechiae and purpura, and epistaxis. Large platelets are seen on peripheral smear. Initial treatment consists of corticosteroids, intravenous gamma globulin, or anti-D immunoglobulin in patients who are Rh positive. Both gamma globulin and anti-D immunoglobulin are rapid in onset. Platelet transfusions are not usually needed unless central nervous system bleeding or active bleeding from other sites occurs. Survival of the transfused platelets is usually short.

Primary immune thrombocytopenia is also known as idiopathic thrombocytopenic purpura (ITP). In children, it is usually acute in onset, short lived, and typically follows a viral illness. In contrast, ITP in adults is gradual in onset, chronic in nature, and has no identifiable cause. Because the circulating platelets in ITP are young and functional, bleeding is less for a given platelet count than when there is failure of platelet production. The pathophysiology of ITP is believed to involve both impaired platelet production and T cell-mediated platelet destruction.¹⁰ Management options are summarized in Table 4-2.¹¹ Treatment of drug-induced immune thrombocytopenia may simply entail withdrawal of the offending drug, but corticosteroids, gamma globulin, and anti-D immunoglobulin may hasten recovery of the count. Heparin-induced thrombocytopenia (HIT) is a form of drug-induced immune thrombocytopenia. It is an immunologic event during which antibodies against platelet factor 4 (PF4) formed during exposure to heparin affect platelet activation and endothelial function with resultant thrombocytopenia and intravascular thrombosis.¹² The platelet count typically begins to fall 5 to 7 days after

Table 4-2

Management of idiopathic thrombocytopenic purpura (ITP) in adults

- First Line**
- a. Corticosteroids: The majority of patients respond but only a few long term
 - b. Intravenous immunoglobulin (IVIG) or anti-D immunoglobulin: indicated for clinical bleeding
- Second Line.** Required in most patients
- a. Splenectomy: open or laparoscopic. Criteria include severe thrombocytopenia, high risk of bleeding, and continued need for steroids. Failure may be due to retained accessory splenic tissue.
 - b. Rituximab, an anti-CD 20 monoclonal antibody
 - c. Thrombopoietin (TPO) receptor agonists such as romiplostim and eltrombopag
- Third Line.** To be used after failure of splenectomy and rituximab
- a. TPO receptor agonists
 - b. Immunosuppressive agents. For failure of TPO receptor agonists

heparin has been started, but if it is a re-exposure, the decrease in count may occur within 1 to 2 days. HIT should be suspected if the platelet count falls to less than 100,000 or if it drops by 50% from baseline in a patient receiving heparin. While HIT is more common with full-dose unfractionated heparin (1%–3%), it can also occur with prophylactic doses or with low molecular weight heparins. Interestingly, approximately 17% of patients receiving unfractionated heparin and 8% receiving low molecular weight heparin develop antibodies against PF4, yet a much smaller percentage develop thrombocytopenia and even fewer develop clinical HIT.¹³ In addition to the mild to moderate thrombocytopenia, this disorder is characterized by a high incidence of thrombosis that may be arterial or venous. Importantly, the absence of thrombocytopenia in these patients does not preclude the diagnosis of HIT.

The diagnosis of HIT may be made by using either a serotonin release assay (SRA) or an enzyme-linked immunosorbent assay (ELISA). The SRA is highly specific but not sensitive, so a positive test supports the diagnosis but a negative test does not exclude HIT.¹² On the other hand, the ELISA has a low specificity, so although a positive ELISA confirms the presence of anti-heparin-PF4, it does not help in the diagnosis of clinical HIT. A negative ELISA, however, essentially rules out HIT.

The initial treatment of suspected HIT is to stop heparin and begin an alternative anticoagulant. Stopping heparin without addition of another anticoagulant is not adequate to prevent thrombosis in this setting. Alternative anticoagulants are primarily thrombin inhibitors. The most recent guideline by the American College of Chest Physicians recommends lepirudin, argatroban, or danaparoid for patients with normal renal function and argatroban for patients with renal insufficiency.¹⁴ Because of warfarin's early induction of a hypercoagulable state, warfarin should be instituted only once full anticoagulation with an alternative agent has been accomplished and the platelet count has begun to recover.

These are also disorders in which thrombocytopenia is a result of platelet activation and formation of platelet thrombi. In thrombotic thrombocytopenic purpura (TTP), large vWF molecules interact with platelets, leading to activation. These large molecules result from inhibition of a metalloproteinase enzyme, ADAMTS13, which cleaves the large vWF molecules.¹⁵ TTP is classically characterized by thrombocytopenia, microangiopathic hemolytic anemia, fever, and renal and neurologic signs or symptoms. The finding of schistocytes on a peripheral blood smear aids in the diagnosis. Plasma exchange with replacement of FFP is the treatment for acute TTP.¹⁶ Additionally, rituximab, a monoclonal antibody against the CD20 protein on B lymphocytes, has shown promise as an immunomodulatory therapy directed against patients with acquired TTP, of which the majority are autoimmune mediated.¹⁷

Hemolytic uremic syndrome (HUS) often occurs secondary to infection by *Escherichia coli* 0157:H7 or other Shiga toxin-producing bacteria. The metalloproteinase is normal in these cases. HUS is usually associated with some degree of renal failure, with many patients requiring renal replacement therapy. Neurologic symptoms are less frequent. A number of patients develop features of both TTP and HUS. This may occur with autoimmune diseases, especially systemic lupus erythematosus and HIV infection, or in association with certain drugs (such as ticlopidine, mitomycin C, gemcitabine) or immunosuppressive agents (such as cyclosporine and tacrolimus). Discontinuation of the involved drug is the mainstay of therapy. Plasmapheresis

is frequently used, but it is not clear what etiologic factor is being removed by the pheresis.

Sequestration is another important cause of thrombocytopenia and usually involves trapping of platelets in an enlarged spleen typically related to portal hypertension, sarcoid, lymphoma, or Gaucher's disease. The total body platelet mass is essentially normal in patients with hypersplenism, but a much larger fraction of the platelets are in the enlarged spleen. Platelet survival is mildly decreased. Bleeding is less than anticipated from the count because sequestered platelets can be mobilized to some extent and enter the circulation. Platelet transfusion does not increase the platelet count as much as it would in a normal person because the transfused platelets are similarly sequestered in the spleen. Splenectomy is not indicated to correct the thrombocytopenia of hypersplenism caused by portal hypertension.

Thrombocytopenia is the most common abnormality of hemostasis that results in bleeding in the surgical patient. The patient may have a reduced platelet count as a result of a variety of disease processes, as discussed earlier. In these circumstances, the marrow usually demonstrates a normal or increased number of megakaryocytes. By contrast, when thrombocytopenia occurs in patients with leukemia or uremia and in patients on cytotoxic therapy, there are generally a reduced number of megakaryocytes in the marrow. Thrombocytopenia also occurs in surgical patients as a result of massive blood loss with product replacement deficient in platelets. Thrombocytopenia may also be induced by heparin administration during cardiac and vascular cases, as in the case of HIT, or may be associated with thrombotic and hemorrhagic complications. When thrombocytopenia is present in a patient for whom an elective operation is being considered, management is contingent upon the extent and cause of platelet reduction. A count of greater than 50,000/ μ L generally requires no specific therapy.

Early platelet administration has now become part of massive transfusion protocols.^{18,19} Platelets are also administered preoperatively to rapidly increase the platelet count in surgical patients with underlying thrombocytopenia. One unit of platelet concentrate contains approximately 5.5×10^{10} platelets and would be expected to increase the circulating platelet count by about 10,000/ μ L in the average 70-kg person. Fever, infection, hepatosplenomegaly, and the presence of antiplatelet alloantibodies decrease the effectiveness of platelet transfusions. In patients refractory to standard platelet transfusion, the use of human leukocyte antigen (HLA)-compatible platelets coupled with special processors has proved effective.

Qualitative Platelet Defects. Impaired platelet function often accompanies thrombocytopenia but may also occur in the presence of a normal platelet count. The importance of this is obvious when one considers that 80% of overall strength is related to platelet function. The life span of platelets ranges from 7 to 10 days, placing them at increased risk for impairment by medical disorders and prescription and over-the-counter medications.

1► Impairment of ADP-stimulated aggregation occurs with massive transfusion of blood products. Uremia may be associated with increased bleeding time and impaired aggregation. Defective aggregation and platelet dysfunction are also seen in patients with thrombocythemia, polycythemia vera, and myelofibrosis.

Drugs that interfere with platelet function include aspirin, clopidogrel, prasugrel, dipyridamole, and GP IIb/IIIa inhibitors. Aspirin, clopidogrel, and prasugrel all irreversibly inhibit

platelet function. Clopidogrel and prasugrel do so through selective irreversible inhibition of ADP-induced platelet aggregation.²⁰ Aspirin works through irreversible acetylation of platelet prostaglandin synthase.

There are no prospective randomized trials in general surgical patients to guide the timing of surgery in patients on aspirin, clopidogrel, or prasugrel.²¹ The general recommendation is that approximately 5 to 7 days should pass from the time the drug is stopped until an elective procedure is performed.²² Timing of urgent and emergent surgeries is even more unclear. Preoperative platelet transfusions may be beneficial, but there are no good data to guide their administration. However, new functional tests are becoming available that may better demonstrate defects in platelet function and may serve to guide the timing of operation or when platelet transfusions might be indicated.

Other disorders associated with abnormal platelet function include uremia, myeloproliferative disorders, monoclonal gammopathies, and liver disease. In the surgical patient, platelet dysfunction of uremia can often be corrected by dialysis or the administration of DDAVP. Platelet transfusion may not be helpful if the patient is uremic when the platelets are given and only serve to increase antibodies. Platelet dysfunction in myeloproliferative disorders is intrinsic to the platelets and usually improves if the platelet count can be reduced to normal with chemotherapy. If possible, surgery should be delayed until the count has been decreased. These patients are at risk for both bleeding and thrombosis. Platelet dysfunction in patients with monoclonal gammopathies is a result of interaction of the monoclonal protein with platelets. Treatment with chemotherapy or, occasionally, plasmapheresis to lower the amount of monoclonal protein improves hemostasis.

Acquired Hypofibrinogenemia

Disseminated Intravascular Coagulation (DIC). DIC is an acquired syndrome characterized by systemic activation of coagulation pathways that result in excessive thrombin generation and the diffuse formation of microthrombi. This disturbance ultimately leads to consumption and depletion of platelets and coagulation factors with the resultant classic picture of diffuse bleeding. Fibrin thrombi developing in the microcirculation may cause microvascular ischemia and subsequent end-organ failure if severe. There are many different conditions that predispose a patient to DIC, and the presence of an underlying condition is required for the diagnosis. For example, injuries resulting in embolization of materials such as brain matter, bone marrow, or amniotic fluid can act as potent thromboplastins that activate the DIC cascade.²³ Additional etiologies include malignancy, organ injury (such as severe pancreatitis), liver failure, certain vascular abnormalities (such as large aneurysms), snake bites, illicit drugs, transfusion reactions, transplant rejection, and sepsis.²⁴ In fact, DIC frequently accompanies sepsis and may be associated with multiple organ failure. As of yet, scoring systems for organ failure do not routinely incorporate DIC. The important interplay between sepsis and coagulation abnormalities was demonstrated by Dhainaut et al who showed that activated protein C was effective in septic patients with DIC.²⁵ The diagnosis of DIC is made based on an inciting etiology with associated thrombocytopenia, prolongation of the prothrombin time, a low fibrinogen level, and elevated fibrin markers (FDPs, D-dimer, soluble fibrin monomers). A scoring system developed by the International Society for Thrombosis and Hemostasis has been shown to have high sensitivity and specificity for diagnosing DIC as well as a strong

correlation between an increasing DIC score and mortality, especially in patients with infections.²⁶

The most important facets of treatment are relieving the patient’s causative primary medical or surgical problem and maintaining adequate perfusion. If there is active bleeding, hemostatic factors should be replaced with FFP, which is usually sufficient to correct the hypofibrinogenemia, although cryoprecipitate, fibrinogen concentrates, or platelet concentrates may also be needed. Given the formation of microthrombi in DIC, heparin therapy has also been proposed. Most studies, however, have shown that heparin is not helpful in acute forms of DIC, but may be indicated in cases where thrombosis predominates, such as arterial or venous thromboembolism and severe purpura fulminans.

Primary Fibrinolysis. An acquired hypofibrinogenic state in the surgical patient can be a result of pathologic fibrinolysis. This may occur in patients following prostate resection when urokinase is released during surgical manipulation of the prostate or in patients undergoing extracorporeal bypass. The severity of fibrinolytic bleeding is dependent on the concentration of breakdown products in the circulation. Antifibrinolytic agents, such as ε-aminocaproic acid and tranexamic acid, interfere with fibrinolysis by inhibiting plasminogen activation.

Myeloproliferative Diseases

Polycythemia, or an excess of red blood cells, places surgical patients at risk. Spontaneous thrombosis is a complication of polycythemia vera, a myeloproliferative neoplasm, and can be explained in part by increased blood viscosity, increased platelet count, and an increased tendency toward stasis. Paradoxically, a significant tendency toward spontaneous hemorrhage also is noted in these patients. Thrombocytosis can be reduced by the administration of low-dose aspirin, phlebotomy, and hydroxyurea.²⁷

Coagulopathy of Liver Disease

The liver plays a key role in hemostasis because it is responsible for the synthesis of many of the coagulation factors (Table 4-3). Patients with liver disease, therefore, have decreased production of several key non-endothelial cell-derived coagulation factors as well as natural anticoagulant proteins, causing a disturbance in the balance between procoagulant and anticoagulant pathways. This disturbance in coagulation mechanisms causes a complex paradigm of both increased bleeding risk and increased thrombotic risk. The most common coagulation abnormalities

Table 4-3

Coagulation factors synthesized by the liver

Vitamin K–dependent factors: II (prothrombin factor), VII, IX, X
Fibrinogen
Factor V
Factor VIII
Factors XI, XII, XIII
Antithrombin III
Plasminogen
Protein C and protein S

associated with liver dysfunction are thrombocytopenia and impaired humoral coagulation function manifested as prolongation of the prothrombin time and international normalized ratio (INR). The etiology of thrombocytopenia in patients with liver disease is typically related to hypersplenism, reduced production of thrombopoietin, and immune-mediated destruction of platelets. The total body platelet mass is often normal in patients with hypersplenism, but a much larger fraction of the platelets is sequestered in the enlarged spleen. Bleeding may be less than anticipated because sequestered platelets can be mobilized to some extent and enter the circulation. Thrombopoietin, the primary stimulus for thrombopoiesis, may be responsible for some cases of thrombocytopenia in cirrhotic patients, although its role is not well delineated. Finally, immune-mediated thrombocytopenia may also occur in cirrhotics, especially those with hepatitis C and primary biliary cirrhosis.²⁸ In addition to thrombocytopenia, these patients also exhibit platelet dysfunction via defective interactions between platelets and the endothelium, and possibly due to uremia and changes in endothelial function in the setting of concomitant renal insufficiency. Hypocoagulopathy is further exacerbated with low platelet counts because platelets help facilitate thrombin generation by assembling coagulation factors on their surfaces. In conditions mimicking intravascular flow, low hematocrit and low platelet counts contributed to decreased adhesion of platelets to endothelial cells, although increased vWF, a common finding in cirrhotic patients, may offset this change in patients with cirrhosis.²⁹ Hypercoagulability of liver disease has recently gained increased attention, with more evidence demonstrating the increased incidence of thromboembolism despite thrombocytopenia and a hypocoagulable state on conventional blood tests.^{30,31} This is attributed to decreased production of liver-synthesized proteins C and S, antithrombin, and plasminogen levels, as well as elevated levels of endothelial-derived vWF and factor VIII, a potent driver of thrombin generation.^{32,33} Given the concomitant hypo- and hypercoagulable features seen in patients with liver disease, conventional coagulation tests may be difficult to interpret, and alternative tests such as thromboelastography (TEG) may be more informative of the functional status of clot formation and stability in cirrhotic patients. Several studies imply that TEG provides a better assessment of bleeding risk than standard tests of hemostasis in patients with liver disease; however, no studies have directly tested this, and future prospective trials are needed.³⁴

Before instituting any therapy to ameliorate thrombocytopenia, the actual need for correction should be strongly considered. In general, correction based solely on a low platelet count should be discouraged. Most often, treatment should be withheld for invasive procedures and surgery. Platelet transfusions are the mainstay of therapy; however, the effect typically lasts only several hours. Risks associated with transfusions in general and the development of antiplatelet antibodies in a patient population likely to need recurrent correction should be considered. A potential alternative strategy involves administration of interleukin-11 (IL-11), a cytokine that stimulates proliferation of hematopoietic stem cells and megakaryocyte progenitors.²⁶ Most studies using IL-11 have been in cancer patients, although some evidence exists that it may be beneficial in cirrhotics as well. Significant side effects limit its usefulness.³⁵ A less well-accepted option is splenectomy or splenic embolization to reduce hypersplenism. In addition to the risks associated with these techniques, reduced splenic blood flow can reduce portal vein flow with subsequent portal vein thrombosis. Results are

mixed following insertion of a transjugular intrahepatic portosystemic shunt (TIPS). Therefore, treatment of thrombocytopenia should not be the primary indication for a TIPS procedure.

Decreased production or increased destruction of coagulation factors as well as vitamin K deficiency can all contribute to a prolonged PT and INR in patients with liver disease. As liver dysfunction worsens, so does the liver's synthetic function, which results in decreased production of coagulation factors. Additionally, laboratory abnormalities may mimic those of DIC. Elevated D-dimers have been reported to increase the risk of variceal bleeding. The absorption of vitamin K is dependent on bile production. Therefore, liver patients with impaired bile production and cholestatic disease may be at risk for vitamin K deficiency.

Similar to thrombocytopenia, correction of coagulopathy should be reserved for treatment of active bleeding and prophylaxis for invasive procedures and surgery. Treatment of coagulopathy caused by liver disease is usually done with FFP, but because the coagulopathy is usually not a result of decreased levels of factor V, complete correction is not usually possible. If the fibrinogen is less than 200 mg/dL, administration of cryoprecipitate may be helpful. Cryoprecipitate is also a source of factor VIII for the rare patient with a low factor VIII level.

Coagulopathy of Trauma

Traditional teaching regarding trauma-related coagulopathy attributed its development to acidosis, hypothermia, and dilution of coagulation factors. Recent data, however, have shown that over one third of injured patients have evidence of coagulopathy at the time of admission.³⁶ More importantly, patients arriving with coagulopathy are at a significantly higher risk of mortality, especially in the first 24 hours after injury. In light of these findings, a dramatic increase in research focused on the optimal management of the acute coagulopathy of trauma (ACoT) has been observed over the past several years. ACoT is not a simple dilutional coagulopathy but a complex problem with multiple mechanisms.³⁷ Whereas multiple contributing factors exist, the key initiators to the process of ACoT are shock and tissue injury. ACoT is a separate and distinct process from DIC, with its own specific components of hemostatic failure. Brohi et al have demonstrated that only patients in shock arrive coagulopathic and that it is the shock that induces coagulopathy through systemic activation of anticoagulant and fibrinolytic pathways.³⁸ As shown in Fig. 4-5, hypoperfusion causes activation of TM on the surface of endothelial cells. Thrombin-TM complexes induce an anticoagulant state through activation of protein C and enhancement of fibrinolysis. This same complex also limits the availability of thrombin to cleave fibrinogen to fibrin, which may explain why injured patients rarely have low levels of fibrinogen.

Acquired Coagulation Inhibitors

Among the most common acquired coagulation inhibitors is the antiphospholipid syndrome (APLS), which includes the lupus anticoagulant and anticardiolipin antibodies. These antibodies may be associated with either venous or arterial thrombosis, or both. In fact, patients presenting with recurrent thrombosis should be evaluated for APLS. Antiphospholipid antibodies are very common in patients with systemic lupus but may also be seen in association with rheumatoid arthritis and Sjögren's syndrome. There are also individuals who will have no autoimmune disorders but develop transient antibodies in response to infections or those who develop drug-induced APLS. The hallmark of

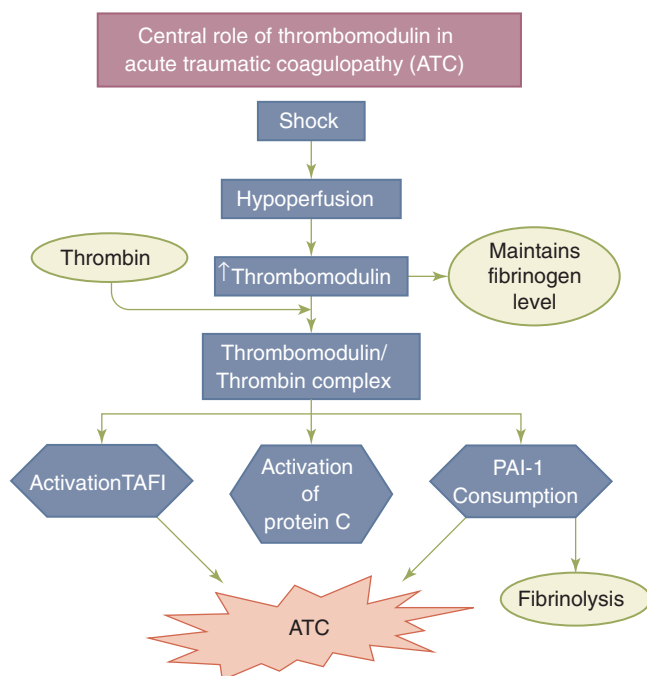


Figure 4-5. Illustration of the pathophysiologic mechanism responsible for the acute coagulopathy of trauma. PAI-1 = plasminogen activator inhibitor 1; TAFI = thrombin-activatable fibrinolysis inhibitor.

APLS is a prolonged aPTT in vitro but an increased risk of thrombosis in vivo.

Anticoagulation and Bleeding

Spontaneous bleeding can be a complication of any anticoagulant therapy whether it is heparin, low molecular weight heparins, warfarin, factor Xa inhibitors, or new direct thrombin inhibitors. The risk of spontaneous bleeding related to heparin is reduced with a continuous infusion technique. Therapeutic anticoagulation is more reliably achieved with a low molecular weight heparin. However, laboratory testing is more challenging with these medications, as they are not detected with conventional coagulation testing. However, their more reliable therapeutic levels (compared to heparin) make them an attractive option for outpatient anticoagulation and more cost-effective for the inpatient setting. If monitoring is required (e.g., in the presence of renal insufficiency or severe obesity), the drug effect should be determined with an assay for anti-Xa activity.

Warfarin is used for long-term anticoagulation in various clinical conditions including deep vein thrombosis, pulmonary embolism, valvular heart disease, atrial fibrillation, recurrent systemic emboli, recurrent myocardial infarction, prosthetic heart valves, and prosthetic implants. Due to the interaction of the P450 system, the anticoagulant effect of the warfarin is reduced (e.g., increases dose required) in patients receiving barbiturates as well as in patients with diets low in vitamin K. Increased warfarin requirements may also be needed in patients taking contraceptives or estrogen-containing compounds, corticosteroids, and adrenocorticotrophic hormone (ACTH). Medications that can alter warfarin requirements are shown in Table 4-4.

Although warfarin use is often associated with a significant increase in morbidity and mortality in acutely injured and emergency surgery patients, with rapid reversal, these complications

Table 4-4

Medications that can alter warfarin dosing

↓ warfarin effect ↑ warfarin requirements	Barbiturates, oral contraceptives, estrogen-containing compounds, corticosteroids, adrenocorticotrophic hormone
↑ warfarin effect ↓ warfarin requirements	Phenylbutazone, clofibrate, anabolic steroids, L-thyroxine, glucagons, amiodarone, quinidine, cephalosporins

can be dramatically reduced. There are several reversal options that include vitamin K administration, plasma, cryoprecipitate, recombinant factor VIIa, and factor concentrates. Urgent reversal for life-threatening bleeding should include vitamin K and a rapid reversal agent such as plasma or prothrombin complex concentrate. In the elderly or those with intracranial hemorrhage, concentrates are preferred, whereas in situations with hypovolemia from hemorrhage, plasma should be used.

Newer anticoagulants like dabigatran and rivaroxaban have no readily available method of detection of the degree of anticoagulation. More concerning is the absence of any available reversal agent. Unlike warfarin, the nonreversible coagulopathy associated with dabigatran and rivaroxaban is of great concern to those providing emergent care to these patients.³⁹

The only possible strategy to reverse the coagulopathy associated with dabigatran may be emergent dialysis. Unfortunately, the ability to rapidly dialyze the hemodynamically unstable bleeding patient or rapidly dialyze the anticoagulated patient with an intracranial bleed is challenging even at large medical centers. Recent data suggest that rivaroxaban, however, may be reversed with the use of prothrombin complex concentrates (four-factor concentrates only: II, VII, IX, and X).⁴⁰ In less urgent states, these drugs can be held for 36 to 48 hours prior to surgery without increased risk of bleeding in those with normal renal function. Alternatively, activated clotting time (stand alone or with rapid TEG) or ecarin clotting time can be obtained in those on dabigatran, and anti-factor Xa assays can be obtained in those taking rivaroxaban.

Bleeding complications in patients on anticoagulants include hematuria, soft tissue bleeding, intracerebral bleeding, skin necrosis, and abdominal bleeding. Bleeding secondary to anticoagulation therapy is also not an uncommon cause of a rectus sheath hematomas. In most of these cases, reversal of anticoagulation is the only treatment that is necessary. Lastly, it is important to remember that symptoms of an underlying tumor may first present with bleeding while on anticoagulation.

Surgical intervention may prove necessary in patients receiving anticoagulation therapy. Increasing experience suggests that surgical treatment can be undertaken without full reversal of the anticoagulant, depending on the procedure being performed.⁴¹ When the aPTT is less than 1.3 times control in a heparinized patient or when the INR is less than 1.5 in a patient on warfarin, reversal of anticoagulation therapy may not be necessary. However, meticulous surgical technique is mandatory, and the patient must be observed closely throughout the postoperative period.

Certain surgical procedures should not be performed in concert with anticoagulation. In particular, cases where even

minor bleeding can cause great morbidity, such as the central nervous system and the eye, surgery should be avoided. Emergency operations are occasionally necessary in patients who have been heparinized. The first step in these patients is to discontinue heparin. For more rapid reversal, protamine sulfate is effective. However, significant adverse reactions, especially in patients with severe fish allergies, may be encountered when administering protamine.⁴² Symptoms include hypotension, flushing, bradycardia, nausea, and vomiting. Prolongation of the aPTT after heparin neutralization with protamine may also be a result of the anticoagulant effect of protamine. In the elective surgical patient who is receiving coumarin-derivative therapy sufficient to effect anticoagulation, the drug can be discontinued several days before operation and the prothrombin concentration then checked (a level >50% is considered safe).⁴³ Rapid reversal of anticoagulation can be accomplished with plasma or prothrombin complex concentrates in the emergent situation. Parenteral administration of vitamin K also is indicated in elective surgical treatment of patients with biliary obstruction or malabsorption who may be vitamin K deficient. However, if low levels of factors II, VII, IX, and X (vitamin K–dependent factors) exist as a result of hepatocellular dysfunction, vitamin K administration is ineffective.

The perioperative management of patients receiving long-term oral anticoagulation therapy is an increasingly common problem. Definitive evidence-based guidelines regarding which patients require perioperative “bridging” anticoagulation and the most effective way to bridge are lacking. However, the American College of Chest Physicians Evidence-Based Clinical Practice Guidelines do serve as best practice for these situations.⁴⁴ A few clinical scenarios exist where the patient should be transitioned to intravenous heparin from oral anticoagulants. A heparin infusion should be held for 4 to 6 hours before the procedure and restarted within 12 to 24 hours of the end of its completion. The primary indication for this level of aggressiveness is patients with mechanical heart valves. Other indications include a recent (within 30 days) myocardial infarction, stroke, or pulmonary embolism. Situations such as thromboembolic events greater than 30 days prior, hypercoagulable history, and atrial fibrillation do not require such stringent restarting strategies.

Cardiopulmonary Bypass. Under normal conditions, homeostasis of the coagulation system is maintained by complex interactions between the endothelium, platelets, and coagulation factors. In patients undergoing cardiopulmonary bypass (CPB), contact with circuit tubing and membranes results in abnormal platelet and clotting factor activation, as well as activation of inflammatory cascades, that ultimately result in excessive fibrinolysis and a combination of both quantitative and qualitative platelet defects. Platelets undergo reversible alterations in morphology and their ability to aggregate, which causes sequestration in the filter, partially degranulated platelets, and platelet fragments. This multifactorial coagulopathy is compounded by the effects of shear stress in the system, induced hypothermia, hemodilution, and anticoagulation.⁴⁵

While on pump, activated clotting time measurements are obtained along with blood gas measurements; however, conventional coagulation assays and platelet counts are not normally performed until rewarming and after a standard dose of protamine has been given. TEG may give a better estimate of the extent of coagulopathy and may also be used to anticipate transfusion requirements if bleeding is present.⁴⁵

Empiric treatment with FFP and cryoprecipitate is often used for bleeding patients; however, there are no universally

accepted transfusion thresholds. Platelet concentrates are given for bleeding patients in the immediate postoperative period; however, studies have shown that indiscriminate platelet therapy conferred no therapeutic advantage.⁴⁶ It is in these patients where rapid coagulation testing is required to assist with directed transfusion therapy.⁴⁷ Many institutions now use antifibrinolytics, such as ϵ -aminocaproic acid and tranexamic acid, at the time of anesthesia induction after several studies have shown that such treatment reduced postoperative bleeding and reoperation. Aprotinin, a protease inhibitor that acts as an antifibrinolytic agent, has been shown to reduce transfusion requirements associated with cardiac surgery.⁴⁸ Desmopressin acetate stimulates release of factor VIII from endothelial cells and may also be effective in reducing blood loss during cardiac surgery. The use of recombinant factor VIIa has also been studied but with conflicting results between improved hemostasis and thrombotic events and mortality, and thus its use is often employed only as a measure of last resort.^{45,49}

Local Hemostasis. Significant surgical bleeding is usually caused by ineffective local hemostasis. The goal is therefore to prevent further blood loss from a disrupted vessel that has been incised or transected. Hemostasis may be accomplished by interrupting the flow of blood to the involved area or by direct closure of the blood vessel wall defect.

Mechanical Procedures. The oldest mechanical method of bleeding cessation is application of direct digital pressure, either at the site of bleeding or proximally to permit more definitive action. An extremity tourniquet that occludes a major vessel proximal to the bleeding site or the Pringle maneuver for liver bleeding are good examples. Direct digital pressure is very effective and has the advantage of being less traumatic than hemostatic or even “atraumatic” clamps.

When a small vessel is transected, a simple ligature is usually sufficient. However, for larger pulsating arteries, a transfixion suture to prevent slipping is indicated. All sutures represent foreign material, and selection should be based on their intrinsic characteristics and the state of the wound. Direct pressure applied by “packing” a wound with gauze or laparotomy pads affords the best method of controlling diffuse bleeding from large areas, such as in the trauma situation. Packing bone wax on the raw surface to effect pressure can control bleeding from cut bone.

Thermal Agents. Heat achieves hemostasis by denaturation of protein that results in coagulation of large areas of tissue. Electrocautery generates heat by induction from an alternating current source, which is then transmitted via conduction from the instrument directly to the tissue. The amplitude setting should be high enough to produce prompt coagulation, but not so high as to set up an arc between the tissue and the cautery tip. This avoids thermal injury outside of the operative field and also prevents exit of current through electrocardiographic leads, other monitoring devices, or permanent pacemakers or defibrillators. A negative grounding plate should be placed beneath the patient to avoid severe skin burns, and caution should be used with certain anesthetic agents (diethyl ether, divinyl ether, ethyl chloride, ethylene, and cyclopropane) because of the hazard of explosion.

A direct current also can result in hemostasis. Because the protein moieties and cellular elements of blood have a negative surface charge, they are attracted to a positive pole where a thrombus is formed. Direct currents in the 20- to 100-mA range have successfully controlled diffuse bleeding from raw surfaces, as has argon gas.

Topical Hemostatic Agents. Topical hemostatic agents can play an important role in helping to facilitate surgical hemostasis. These agents are classified based on their mechanism of action, and many act at specific stages in the coagulation cascade and take advantage of natural physiologic responses to bleeding.⁵⁰ The ideal topical hemostatic agent has significant hemostatic action, minimal tissue reactivity, nonantigenicity, in vivo biodegradability, ease of sterilization, low cost, and can be tailored to specific needs.⁵¹

In 2010, Achneck et al published a comprehensive overview of absorbable, biologic, and synthetic agents.⁵² Absorbable agents include gelatin foams (Gelfoam), oxidized cellulose (Surgicel), and microfibrillar collagens (Avitene). Both gelatin foam and oxidized cellulose provide a physical matrix for clotting initiation, while microfibrillar collagens facilitate platelet adherence and activation. Biologic agents include topical thrombin, fibrin sealants (FloSeal), and platelet sealants (Vita-gel). Human or recombinant thrombin derivatives, which facilitate the formation of fibrin clots and subsequent activation of several clotting factors, take advantage of natural physiologic processes, thereby avoiding foreign body or inflammatory reactions.⁵¹ Caution must be taken in judging vessel caliber in the wound because thrombin entry into larger caliber vessels can result in systemic exposure to thrombin with a risk of disseminated intravascular clotting or death. They are particularly effective in controlling capillary bed bleeding when pressure or ligation is insufficient; however, the bovine derivatives should be used with caution due to the potential immunologic response and worsened coagulopathy. Fibrin sealants are prepared from cryoprecipitate (homologous or synthetic) and have the advantage of not promoting inflammation or tissue necrosis.⁵³ Platelet sealants are a mixture of collagen and thrombin combined with plasma-derived fibrinogen and platelets from the patient, which requires the additional need for centrifugation and processing.

Topical agents are not a substitute for meticulous surgical technique and only function as adjuncts to help facilitate surgical hemostasis. The advantages and disadvantages of each agent must be considered, and use should be limited to the minimum amount necessary to minimize toxicity, adverse reactions, interference with wound healing, and procedural costs.

TRANSFUSION

Background

Human blood replacement therapy was accepted in the late nineteenth century. This was followed by the introduction of blood grouping by Landsteiner who identified the major A, B, and O groups in 1900, resulting in widespread use of blood products in World War I. Levine and Stetson in 1939 followed with the concept of Rh grouping. These breakthroughs established the foundation from which the field of transfusion medicine has grown. Whole blood was considered the standard in transfusion until the late 1970s when component therapy began to take prominence. This change in practice was made possible by the development of improved collection strategies, infectious disease testing, and advances in preservative solutions and storage.

Replacement Therapy

Typing and Cross-Matching. Serologic compatibility for A, B, O, and Rh groups is established routinely. Cross-matching between the donors' red blood cells and the recipients' sera (the major cross-match) is performed. Rh-negative recipients should

be transfused only with Rh-negative blood. However, this group represents only 15% of the population. Therefore, the administration of Rh-positive blood is acceptable if Rh-negative blood is not available. However, Rh-positive blood should not be transfused to Rh-negative females who are of child-bearing age.

In emergency situations, type O-negative blood may be transfused to all recipients. O-negative and type-specific red blood cells are equally safe for emergency transfusion. Problems are associated with the administration of four or more units of O-negative blood because there is a significant increase in the risk of hemolysis. In patients with clinically significant cold agglutinins, blood should be administered through a blood warmer. If these antibodies are present in high titer, hypothermia is contraindicated.

In patients who have been multiply transfused and who have developed alloantibodies or who have autoimmune hemolytic anemia with pan-red blood cell antibodies, typing and cross-matching is often difficult, and sufficient time should be allotted preoperatively to accumulate blood that might be required during the operation. Cross-matching should always be performed before the administration of dextran because it interferes with the typing procedure.

The use of autologous transfusion is growing. Up to 5 units can be collected for subsequent use during elective procedures. Patients can donate and store their own blood if their hemoglobin concentration exceeds 11 g/dL or if the hematocrit is greater than 34%. The first procurement is performed 40 days before the planned operation, and the last one is performed 3 days before the operation. Donations can be scheduled at intervals of 3 to 4 days. Recombinant human erythropoietin (rHuEPO) accelerates generation of red blood cells and allows for more frequent harvesting of blood.

Banked Whole Blood. Once the gold standard, whole blood is rarely available in Western countries. With sequential changes in storage solutions, the shelf life of red blood cells is now 42 days. Recent evidence has demonstrated that the age of red cells may play a significant role in the inflammatory response and incidence of multiple organ failure.⁵⁴ The changes in the red blood cells that occur during storage include reduction of intracellular ADP and 2,3-diphosphoglycerate (2,3-DPG), which alters the oxygen dissociation curve of hemoglobin, resulting in a decrease in oxygen transport. Stored RBCs progressively becomes acidotic with elevated levels of lactate, potassium, and ammonia.

Red Blood Cells and Frozen Red Blood Cells. Red blood cells are the product of choice for most clinical situations requiring resuscitation. Concentrated suspensions of red blood cells can be prepared by removing most of the supernatant plasma after centrifugation. The preparation reduces but does not eliminate reactions caused by plasma components. Frozen red blood cells are not currently available for use in emergencies, as the thawing and preparation time is measured in hours. They are used for patients who are known to have been previously sensitized. The red blood cell viability is improved, and the ATP and 2,3-DPG concentrations are maintained.

Leukocyte-Reduced and Leukocyte-Reduced/Washed Red Blood Cells. These products are prepared by filtration that removes about 99.9% of the white blood cells and most of the platelets (leukocyte-reduced red blood cells) and, if necessary, by additional saline washing (leukocyte-reduced/washed red blood cells). Leukocyte reduction prevents almost all febrile,

nonhemolytic transfusion reactions (fever and/or rigors), alloimmunization to HLA class I antigens, and platelet transfusion refractoriness and cytomegalovirus transmission. In most Western nations, it is the standard red blood cell transfusion product. Supporters of universal leukocyte reduction argue that allogenic transfusion of white cells predisposes to postoperative bacterial infection and multiorgan failure. Reviews of randomized trials and meta-analyses have not provided convincing evidence either way,^{55,56} although a large Canadian retrospective study suggests a decrease in mortality and infections.⁵⁷

Platelet Concentrates. The indications for platelet transfusion include thrombocytopenia caused by massive blood loss and replacement with platelet-poor products, thrombocytopenia caused by inadequate production, and qualitative platelet disorders. The shelf life of platelets is 120 hours from time of donation. One unit of platelet concentrate has a volume of approximately 50 mL. Platelet preparations are capable of transmitting infectious diseases and can account for allergic reactions similar to those caused by red blood cell transfusion. A therapeutic level of platelets is in the range of 50,000 to 100,000/ μ L but is very dependent on the clinical situation. Recent evidence suggests that earlier use of platelets may improve outcomes in bleeding patients.⁵⁸

In rare cases, in patients who become alloimmunized through previous transfusion or patients who are refractory from sensitization through prior pregnancies, HLA-matched platelets can be used.

Fresh Frozen Plasma. Fresh frozen plasma (FFP) prepared from freshly donated blood is the usual source of the vitamin K-dependent factors and is the only source of factor V. FFP carries similar infectious risks as other component therapies. Use of plasma as a primary resuscitation modality in patients who are rapidly bleeding has received attention over the last few years, and ongoing studies are under way to evaluate this concept. FFP can be thawed and stored for up to 5 days, greatly increasing its immediate availability. In an effort to increase the shelf life and avoid the need for refrigeration, lyophilized plasma is being tested. Preliminary animal studies suggest that it preserves the beneficial effects of FFP.⁵⁹

Concentrates and Recombinant DNA Technology. Technologic advancements have made the majority of clotting factors and albumin readily available as concentrates. These products are readily available and carry none of the inherent infectious risks as other component therapies.

Tranexamic Acid. Tranexamic acid (TXA; trade name: Cyklokapron), an antifibrinolytic agent, has been used to decrease bleeding and the need for blood transfusions in coronary artery bypass grafting (CABG), orthotopic liver transplantation, hip and knee arthroplasty, and other surgical settings. The safety and efficacy of using TXA to treat trauma patients was recently evaluated in a large randomized, placebo-controlled clinical trial.⁶⁰ In this trial, 20,211 adult trauma patients in 274 hospitals in 40 countries with significant hemorrhage (heart rate >110 beats per minute and systolic blood pressure <90 mmHg or both) or judged to be at risk for significant hemorrhage were randomized to either TXA or placebo administered as a loading dose of 1 g over 10 minutes followed by an infusion of 1 g over 8 hours. It is important to understand that the responsible physician did not randomize patients with either a clear indication or a clear contraindication to TXA. The overall mortality rate in the cohort studied was 15.3%, of whom 35.3% died on the day of randomization. A total of 1063 patients died due to

hemorrhage, and the majority died on the day of randomization. The authors reported that TXA use resulted in a statistically significant reduction in the relative risk (RR) of all-cause mortality of 9% (14.5 vs. 16.0%, RR 0.91, confidence interval [CI] 0.85–0.97; $P = .0035$). A recent post hoc analysis of the CRASH-2 data showed that the greatest benefit of TXA administration occurred when patients received the medication soon after injury.⁶¹ In this analysis, TXA given between 1 and 3 hours after trauma reduced the risk of death due to bleeding by 21% (147/3037 [4.8%] vs. 184/2996 [6.1%], RR 0.79, CI 0.64–0.97; $P = .03$). Treatment given after 3 hours increased the risk of death due to bleeding (144/3272 [4.4%] vs. 103/3362 [3.1%], RR 1.44, CI 1.12–1.84; $P = .004$). Finally, a recent meta-analysis reported that TXA is effective for preventing blood loss in surgery and reducing transfusion and was not associated with increased vascular occlusive events.⁶²

Adverse events associated with TXA use have been reported. These include acute gastrointestinal disturbances (nausea, vomiting, and diarrhea, generally dose-related), visual disturbances (blurry vision and changes in color perception, especially with prolonged use), and occasional thromboembolic events (e.g., deep venous thrombosis and pulmonary embolism, generally observed in the setting of active intravascular clotting). Its use is thus contraindicated in the settings of acquired defective color vision and active intravascular clotting. TXA should be used with caution in the setting of urinary tract bleeding because ureteral obstruction due to clotting has been reported. TXA is contraindicated in patients with aneurysmal subarachnoid hemorrhage; however, there have been no reported complications associated with intra- or extracranial hemorrhage associated with trauma. TXA should not be given with activated prothrombin complex concentrate or factor IX complex concentrates because these may increase the risk of thrombosis.

TXA is an antifibrinolytic that inhibits both plasminogen activation and plasmin activity, thus preventing clot breakdown rather than promoting new clot formation. TXA is an inhibitor of plasminogen activation and an inhibitor of plasmin activity. It occupies the lysine binding sites on plasminogen, thus preventing its binding to lysine residues on fibrin. This reduces plasminogen activation to plasmin. Similarly, blockade of lysine-binding sites on circulating plasmin prevents binding to fibrin and thus prevents clot breakdown. TXA is 10 times more potent in vitro than aminocaproic acid. At therapeutically relevant concentrations, TXA does not affect platelet count or aggregation or coagulation parameters. It is excreted largely unchanged in urine and has a half-life of about 2 hours in circulation. While prolonged use requires that dosing be adjusted for renal impairment, use in the acute trauma situation does not appear to require adjustment. No adjustment is needed for hepatic impairment. Based on the CRASH-2 trial, TXA is becoming more widely used in the United States for patients with ongoing bleeding, especially those with documented evidence of fibrinolysis. Careful analysis of recently ongoing trials will further elucidate the safety profile of this powerful drug.⁶³

Indications for Replacement of Blood and Its Elements

Improvement in Oxygen-Carrying Capacity. Oxygen-carrying capacity is primarily a function of the red blood cells. Thus, transfusion of red blood cells should augment oxygen-carrying capacity. Additionally, hemoglobin is fundamental to

arterial oxygen content and thus oxygen delivery. Despite this obvious association, there is little evidence that actually supports the premise that transfusion of red blood cells equates with enhanced cellular delivery and utilization. The reasons for this apparent discrepancy are related to changes that occur with storage of blood. The decrease in 2,3-DPG and P50 impair oxygen offloading, and deformation of the red cells impairs microcirculatory perfusion.⁶⁴

Treatment of Anemia: Transfusion Triggers. A 1988 National Institutes of Health Consensus Report challenged the dictum that a hemoglobin value of less than 10 g/dL or a hematocrit level less than 30% indicates a need for preoperative red blood cell transfusion. This was verified in a prospective randomized controlled trial in critically ill patients that compared a restrictive transfusion threshold to a more liberal strategy and demonstrated that maintaining hemoglobin levels between 7 and 9 g/dL had no adverse effect on mortality. In fact, patients with APACHE II scores of ≤ 20 or patients age < 55 years actually had a lower mortality.⁶⁵

Despite these results, change in daily clinical practice has been slow. Critically ill patients still frequently receive transfusions, with the pretransfusion hemoglobin approaching 9 g/dL in a recent large observational study.⁶⁶ This outdated approach unnecessarily exposes patients to increased risk and little benefit.

One unresolved issue related to transfusion triggers is the safety of maintaining a hemoglobin of 7 g/dL in a patient with ischemic heart disease. Data on this subject are mixed, and many studies have significant design flaws, including their retrospective nature. However, the majority of the published data favors a restrictive transfusion trigger for patients with non-ST elevation acute coronary syndrome, with many reporting worse outcomes in those patients receiving transfusions.^{67,68}

Volume Replacement

The most common indication for blood transfusion in surgical patients is the replenishment of the blood volume; however, a deficit is difficult to evaluate. Measurements of hemoglobin or hematocrit levels are frequently used to assess blood loss. These measurements can be occasionally misleading in the face of acute loss. Both the amount and the rate of bleeding are factors in the development of signs and symptoms of blood loss.

Loss of blood in the operating room can be roughly evaluated by estimating the amount of blood in the wound and on the drapes, weighing the sponges, and quantifying blood suctioned from the operative field. In patients with normal preoperative values, blood loss up to 20% of total blood volume can be replaced with crystalloid or colloid solutions. Blood loss above this value may require the addition of a balanced resuscitation including red blood cells, FFP, and platelets (detailed later in this chapter) (Table 4-5).

New Concepts in Resuscitation

Traditional resuscitation algorithms are sequentially based on crystalloid followed by red blood cells and then plasma and platelet transfusions and have been in widespread use since the 1970s. No quality clinical data supported this concept. Recently the damage control resuscitation (DCR) strategy, aimed at halting and/or preventing rather than treating the lethal triad of coagulopathy, acidosis, and hypothermia, has challenged traditional thinking on early resuscitation strategies.⁶⁹

Rationale. In civilian trauma systems, nearly half of all deaths happen before a patient reaches the hospital, and many

are nonpreventable.⁷⁰ Patients who survive to an emergency center have a high incidence of truncal hemorrhage, and deaths in this group of patients may be potentially preventable. Truncal hemorrhage patients in shock often present with the early coagulopathy of trauma in the emergency department and are at significant risk of dying.⁷¹⁻⁷³

Many of these patients have suffered substantial bleeding and may receive a significant transfusion, generally defined as the administration of ≥ 4 to 6 units of red blood cells within 4 to 6 hours of admission. This definition is admittedly arbitrary. Although 25% of all trauma admissions receive a unit of blood early after admission, only a small percentage of patients receive a massive transfusion. In the military setting, the percentage of massive transfusion patients almost doubles.⁷⁴

Damage Control Resuscitation. Standard advanced trauma life support guidelines start resuscitation with crystalloid, followed by packed red blood cells.⁷⁵ Only after several liters of crystalloid have been transfused does transfusion of units of plasma or platelets begin. This conventional massive transfusion practice was based on a several small uncontrolled retrospective studies that used blood products containing increased amounts of plasma, which are no longer available.⁷⁶ Because of the known early coagulopathy of trauma, the current approach to managing the exsanguinating patient involves early implementation of damage control resuscitation (DCR). Although most of the attention to hemorrhagic shock resuscitation has centered on higher ratios of plasma and platelets, DCR is actually composed of three basic components: permissive hypotension, minimizing crystalloid-based resuscitation, and the immediate release and administration of predefined blood products (red blood cells, plasma, and platelets) in ratios similar to those of whole blood.

In Iraq and Afghanistan, DCR practices are demonstrating unprecedented success with improved overall survival.⁷⁷ Civilian data also suggest that a balanced resuscitation approach yields improved outcome in severely injured and bleeding trauma patients.⁶⁹ To verify military and single-institution civilian data on DCR, a multicenter retrospective study of modern transfusion practice at 17 leading civilian trauma centers was performed.⁷⁸ It was found that plasma:platelet:red blood cell ratios varied from 1:1:1 to 0.3:0.1:1, with corresponding survival rates ranging from 71% to 41%. A significant center effect was seen, documenting wide variation in both transfusion practice and outcomes between Level 1 trauma centers. This variation correlated with blood product ratios. Increased plasma- and platelet-to-RBC ratios significantly decreased truncal hemorrhagic death and 30-day mortality without a concomitant increase in multiple organ failure as a cause of death. A prospective observational study evaluating current transfusion practice at 10 Level 1 centers was recently published, again documenting the wide variability in practice and improved outcomes with earlier use of increased ratios of plasma and platelets.⁷⁹ Patients receiving ratios less than 1:2 were four times more likely to die than patients with ratios of 1:1 or higher.

Regardless of the optimal ratio, it is essential that the trauma center has an established mechanism to deliver these products quickly and in the correct amounts to these critically injured patients. In fact, several authors have shown that a well-developed massive transfusion protocol is associated with improved outcomes independent of the ratios chosen.⁸⁰ This aggressive delivery of predefined blood products should begin prior to any laboratory-defined anemia or coagulopathy.

Table 4-5

Replacement of clotting factors

FACTOR	NORMAL LEVEL	LIFE SPAN IN VIVO (HALF-LIFE)	FATE DURING COAGULATION	LEVEL REQUIRED FOR SAFE HEMOSTASIS	IDEAL AGENT ACD BANK BLOOD (4°C [39.2°F])	IDEAL AGENT FOR REPLACING DEFICIT
I (fibrinogen)	200–400 mg/100 mL	72 h	Consumed	60–100 mg/100 mL	Very stable	Bank blood; concentrated fibrinogen
II (prothrombin)	20 mg/100 mL (100% of normal level)	72 h	Consumed	15%–20%	Stable	Bank blood; concentrated preparation
V (proaccelerin, accelerator globulin, labile factor)	100% of normal level	36 h	Consumed	5%–20%	Labile (40% of normal level at 1 wk)	Fresh frozen plasma; blood under 7 d
VII (proconvertin, serum prothrombin conversion accelerator, stable factor)	100% of normal level	5 h	Survives	5%–30%	Stable	Bank blood; concentrated preparation
VIII (antihemophilic factor, antihemophilic globulin)	100% of normal level (50%–150% of normal level)	6–12 h	Consumed	30%	Labile (20%–40% of normal level at 1 wk)	Fresh frozen plasma; concentrated antihemophilic factor; cryoprecipitate
IX (Christmas factor, plasma thromboplastin component)	100% of normal level	24 h	Survives	20%–30%	Stable	Fresh-frozen plasma; bank blood; concentrated preparation
X (Stuart-Prower factor)	100% of normal level	40 h	Survives	15%–20%	Stable	Bank blood; concentrated preparation
XI (plasma thromboplastin antecedent)	100% of normal level	Probably 40–80 h	Survives	10%	Probably stable	Bank blood
XII (Hageman factor)	100% of normal level	Unknown	Survives	Deficit produces no bleeding tendency	Stable	Replacement not required
XIII (fibrinase, fibrin-stabilizing factor)	100% of normal level	4–7 d	Survives	Probably <1%	Stable	Bank blood
Platelets	150,000–400,000/μL	8–11 d	Consumed	60,000–100,000/μL	Very labile (40% of normal level at 20 h; 0 at 48 h)	Fresh blood or plasma; fresh platelet concentrate (not frozen plasma)

ACD = acid-citrate-dextrose.

Source: Reproduced with permission from Salzman EW: Hemorrhagic disorders. In: Kinney JM, Egdahl RH, Zuidema GD, eds. *Manual of Preoperative and Postoperative Care*. 2nd ed. Philadelphia: WB Saunders; 1971:157. Copyright Elsevier.

Table 4-6

Adult Transfusion Clinical Practice Guideline**A. Initial Transfusion of Red Blood Cells (RBCs):**

1. Notify blood bank immediately of urgent need for RBCs.
O negative uncross-matched (available immediately).
As soon as possible, switch to O negative for females and O positive for males.
Type-specific uncross-matched (available in approximately 5–10 min).
Completely cross-matched (available in approximately 40 min).
2. A blood sample must be sent to blood bank for a type and cross.
3. The Emergency Release of Blood form must be completed. If the blood type is not known and blood is needed immediately, O-negative RBCs should be issued.
4. RBCs will be transfused in the standard fashion. All patients must be identified (name and number) prior to transfusion.
5. Patients who are unstable or receive 1–2 RBCs and do not rapidly respond should be considered candidates for the massive transfusion (MT) guideline.

B. Adult Massive Transfusion Guideline:

1. The Massive Transfusion Guideline (MTG) should be initiated as soon as it is anticipated that a patient will require massive transfusion (≥ 10 U RBCs in 24 h). The Blood Bank should strive to deliver plasma, platelets, and RBCs in a 1:1:1 ratio. To be effective and minimize further dilutional coagulopathy, the 1:1:1 ratio must be initiated early, ideally with the first 2 units of transfused RBCs. Crystalloid infusion should be minimized.
2. Once the MTG is activated, the Blood Bank will have 6 RBCs, 6 FFP, and a 6 pack of platelets packed in a cooler available for rapid transport. If 6 units of thawed FFP are not immediately available, the Blood Bank will issue units that are ready and notify appropriate personnel when the remainder is thawed. Every attempt should be made to obtain a 1:1:1 ratio of plasma:platelets:RBCs.
3. Once initiated, the MT will continue until stopped by the attending physician. MT should be terminated once the patient is no longer actively bleeding.
4. No blood components will be issued without a pickup slip with the recipient's medical record number and name.
5. Basic laboratory tests should be drawn immediately on ED arrival and optimally performed on point-of-care devices, facilitating timely delivery of relevant information to the attending clinicians. These tests should be repeated as clinically indicated (e.g., after each cooler of products has been transfused). Suggested laboratory values are:
 - CBC
 - INR, fibrinogen
 - pH and/or base deficit
 - TEG, where available

CBC = complete blood count; ED = emergency department; FFP = fresh frozen plasma; INR = international normalized ratio; TEG = thromboelastography.

An example of an adult massive transfusion clinical guideline specifying the early use of component therapy is shown in Table 4-6. Specific recommendations for the administration of component therapy during a massive transfusion are shown in Table 4-7. Because only a small percentage of trauma patients require a massive transfusion and because blood products in general are in short supply, the need for early prediction models has been studied and a comparison of results from both civilian and military studies is shown in Table 4-8.⁸¹⁻⁸⁵ While compelling, none of these algorithms have been prospectively validated.

Complications of Transfusion (Table 4-9)

Transfusion-related complications are primarily related to blood-induced proinflammatory responses. Transfusion-related events are estimated to occur in approximately 10% of all transfusions, but less than 0.5% are serious in nature. Transfusion-related deaths, although rare, do occur and are related primarily to transfusion-related acute lung injury (TRALI) (16%–22%), ABO hemolytic transfusion reactions (12%–15%), and bacterial contamination of platelets (11%–18%).⁸⁶

Nonhemolytic Reactions. Febrile, nonhemolytic reactions are defined as an increase in temperature ($>1^{\circ}\text{C}$) associated with a transfusion and are fairly common (approximately 1% of all

transfusions). Preformed cytokines in donated blood and recipient antibodies reacting with donated antibodies are postulated etiologies. The incidence of febrile reactions can be greatly reduced by the use of leukocyte-reduced blood products. Pretreatment with acetaminophen reduces the severity of the reaction.

Bacterial contamination of infused blood is rare. Gram-negative organisms, which are capable of growth at 4°C , are the most common cause. Most cases, however, are associated with the administration of platelets that are stored at 20°C or, even more commonly, with apheresis platelets stored at room temperature. Cases from FFP thawed in contaminated water baths have also been reported.⁸⁷ Bacterial contamination can result in sepsis and death in up to 25% of patients.⁸⁸ Clinical manifestations include systemic signs such as fever and chills, tachycardia and hypotension, and gastrointestinal symptoms (abdominal cramps, vomiting, and diarrhea). If the diagnosis is suspected, the transfusion should be discontinued and the blood cultured. Emergency treatment includes oxygen, adrenergic blocking agents, and antibiotics.

Allergic Reactions. Allergic reactions are relatively frequent, occurring in about 1% of all transfusions. Reactions are usually mild and consist of rash, urticaria, and flushing. In rare instances, anaphylactic shock develops. Allergic reactions are

Table 4-7

Component therapy administration during massive transfusion

Fresh frozen plasma (FFP)	As soon as the need for massive transfusion is recognized. For every 6 red blood cells (RBCs), give 6 FFP (1:1 ratio).
Platelets	For every 6 RBCs and plasma, give one 6 pack of platelets. 6 random-donor platelet packs = 1 apheresis platelet unit. Platelets are in every cooler. Keep platelet counts >100,000.
Cryoprecipitate	After first 6 RBCs, check fibrinogen level. If ≤ 200 mg/dL, give 20 units cryoprecipitate (2 g fibrinogen). Repeat as needed, depending on fibrinogen level, and request appropriate amount of cryoprecipitate.

caused by the transfusion of antibodies from hypersensitive donors or the transfusion of antigens to which the recipient is hypersensitive. Allergic reactions can occur after the administration of any blood product but are commonly associated with FFP and platelets. Treatment and prophylaxis consist of the administration of antihistamines. In more serious cases, epinephrine or steroids may be indicated.

Respiratory Complications. Respiratory compromise may be associated with transfusion-associated circulatory overload (TACO), which is an avoidable complication. It can occur with rapid infusion of blood, plasma expanders, and crystalloids, particularly in older patients with underlying heart disease. Central venous pressure monitoring should be considered whenever large amounts of fluid are administered. Overload is manifest by a rise in venous pressure, dyspnea, and cough. Rales can generally be heard at the lung bases. Treatment consists of diuresis, slowing the rate of blood administration, and minimizing fluids while blood products are being transfused.

Table 4-8

Comparison of massive transfusion prediction studies

AUTHOR	VARIABLES	ROC AUC VALUE
McLaughlin et al ⁸¹	SBP, HR, pH, Hct	0.839
Yücel et al ⁸²	SBP, HR, BD, Hgb, Male, + FAST, long bone/pelvic fracture	0.892
Moore et al ⁸³	SBP, pH, ISS >25	0.804
Schreiber et al ⁸⁴	Hgb ≤ 11 , INR >1.5, penetrating injury	0.80
Cotton et al ⁸⁵	HR, SBP, FAST, penetrating injury	0.83-0.90

AUC = area under the curve; BD = base deficit; FAST = Focused assessment with sonography for trauma; Hct = hematocrit; Hgb = hemoglobin; HR = heart rate; INR = international normalized ratio; ISS = injury severity score; ROC = receiver operating characteristic; SBP = systolic blood pressure.

The syndrome of TRALI is defined as noncardiogenic pulmonary edema related to transfusion.⁸⁹ It can occur with the administration of any plasma-containing blood product. Symptoms are similar to circulatory overload with dyspnea and associated hypoxemia. However, TRALI is characterized as noncardiogenic and is often accompanied by fever, rigors, and bilateral pulmonary infiltrates on chest x-ray. It most commonly occurs within 1 to 2 hours after the onset of transfusion but virtually always before 6 hours. Toy et al recently reported a decrease in the incidence of TRALI with the reduction transfusion of plasma from female donors, due to a combination of reduced transfusion of strong cognate HLA class II antibodies and HNA antibodies in patients with risk factors for acute lung injury.⁹⁰ Treatment of TRALI entails discontinuation of any transfusion, notification of the transfusion service, and pulmonary support, which may vary from supplemental oxygen to mechanical ventilation.

Hemolytic Reactions. Hemolytic reactions can be classified as either acute or delayed. Acute hemolytic reactions occur with the administration of ABO-incompatible blood and can be fatal in up to 6% of cases. Contributing factors include errors in the laboratory of a technical or clerical nature or the administration of the wrong blood type. Immediate hemolytic reactions are characterized by intravascular destruction of red blood cells and consequent hemoglobinemia and hemoglobinuria. DIC can be initiated by antibody-antigen complexes activating factor XII and complement, leading to activation of the coagulation cascade. Finally, acute renal insufficiency results from the toxicity associated with free hemoglobin in the plasma, resulting in tubular necrosis and precipitation of hemoglobin within the tubules.

Delayed hemolytic transfusion reactions occur 2 to 10 days after transfusion and are characterized by extravascular hemolysis, mild anemia, and indirect (unconjugated) hyperbilirubinemia. They occur when an individual has a low antibody titer at the time of transfusion, but the titer increases after transfusion as a result of an anamnestic response. Reactions to non-ABO antigens involve immunoglobulin G-mediated clearance by the reticuloendothelial system.

If the patient is awake, the most common symptoms of acute transfusion reactions are pain at the site of transfusion, facial flushing, and back and chest pain. Associated symptoms include fever, respiratory distress, hypotension, and tachycardia. In anesthetized patients, diffuse bleeding and hypotension are the hallmarks. A high index of suspicion is needed to make the diagnosis. The laboratory criteria for a transfusion reaction are hemoglobinuria and serologic criteria that show incompatibility of the donor and recipient blood. A positive Coombs' test indicates transfused cells coated with patient antibody and is diagnostic. Delayed hemolytic transfusions may also be manifest by fever and recurrent anemia. Jaundice and decreased haptoglobin usually occur, and low-grade hemoglobinemia and hemoglobinuria may be seen. The Coombs' test is usually positive, and the blood bank must identify the antigen to prevent subsequent reactions.

If an immediate hemolytic transfusion reaction is suspected, the transfusion should be stopped immediately, and a sample of the recipient's blood drawn and sent along with the suspected unit to the blood bank for comparison with the pretransfusion samples. Urine output should be monitored and adequate hydration maintained to prevent precipitation of hemoglobin within the tubules. Delayed hemolytic transfusion reactions do not usually require specific intervention.

Table 4-9

Transfusion-related complications

ABBREVIATION	COMPLICATION	SIGNS AND SYMPTOMS	FREQUENCY	MECHANISM	PREVENTION
NHTR	Febrile, nonhemolytic transfusion reaction	Fever	0.5%–1.5% of transfusions	Preformed cytokines Host Ab to donor lymphocytes	Use leukocyte-reduced blood Store platelets <5 d
	Bacterial contamination	High fever, chills Hemodynamic changes DIC Emesis, diarrhea Hemoglobinuria	<<0.05% of blood 0.05% of platelets	Infusion of contaminated blood	
	Allergic reactions	Rash, hives Itching	0.1%–0.3% of units	Soluble transfusion constituents	Provide antihistamine prophylaxis
TACO	Transfusion-associated circulatory overload	Pulmonary edema	? 1:200–1:10,00 of transfused patients	Large volume of blood transfused into an older patient with CHF	Increase transfusion time Administer diuretics Minimize associated fluids
TRALI	Transfusion-related acute lung injury	Acute (<6 h) hypoxemia Bilateral infiltrates ± Tachycardia, hypotension		Anti-HLA or anti-HNA Ab in transfused blood attacks circulatory and pulmonary leukocytes	Limit female donors
	Hemolytic reaction, acute	Fever Hypotension DIC Hemoglobinuria Hemoglobinemia Renal insufficiency	1:33,000–1:1,500,000 units	Transfusion of ABO-incompatible blood Preformed IgM Ab to ABO Ag	Transfuse appropriately matched blood
	Hemolytic reaction, delayed (2–10 d)	Anemia Indirect hyperbilirubinemia Decreased haptoglobin level Positive result on direct Coombs' test		IgG mediated	Identify patient's Ag to prevent recurrence

Ab = antibody; Ag = antigen; CHF = congestive heart failure; DIC = disseminated intravascular coagulation; HLA = human leukocyte antigen; HNA = anti-human neutrophil antigen; IgG = immunoglobulin G; IgM = immunoglobulin M.

Transmission of Disease. Malaria, Chagas' disease, brucellosis, and, very rarely, syphilis are among the diseases that have been transmitted by transfusion. Malaria can be transmitted by all blood components. The species most commonly implicated is *Plasmodium malariae*. The incubation period ranges from 8 to 100 days; the initial manifestations are shaking chills and spiking fever. Cytomegalovirus (CMV) infection resembling infectious mononucleosis also has occurred.

Transmission of hepatitis C and HIV-1 has been dramatically minimized by the introduction of better antibody and nucleic acid screening for these pathogens. The residual risk among allogeneic donations is now estimated to be less than 1 per 1,000,000 donations. The residual risk of hepatitis B is approximately 1 per 300,000 donations.⁹¹ Hepatitis A is very rarely transmitted because there is no asymptomatic carrier state. Improved donor selection and testing are responsible for

the decreased rates of transmission. Recent concerns about the rare transmission of these and other pathogens, such as West Nile virus, are being addressed by current trials of "pathogen inactivation systems" that reduce infectious levels of all viruses and bacteria known to be transmittable by transfusion. Prion disorders (e.g., Creutzfeldt-Jakob disease) also are transmissible by transfusion, but there is currently no information on inactivation of prions in blood products for transfusion.

TESTS OF HEMOSTASIS AND BLOOD COAGULATION

The initial approach to assessing hemostatic function is a careful review of the patient's clinical history (including previous abnormal bleeding or bruising), drug use, and basic laboratory testing. Common screening laboratory testing includes platelet count, PT or INR, and aPTT. Platelet dysfunction can occur

at either extreme of platelet count. The normal platelet count ranges from 150,000 to 400,000/ μL . Whereas a platelet count greater than 1,000,000/ μL may be associated with bleeding or thrombotic complications, increased bleeding complications may be observed with major surgical procedures when the platelets are below 50,000/ μL and with minor surgical procedures when counts are below 30,000/ μL , and spontaneous hemorrhage can occur when the counts fall below 20,000/ μL . Despite a lack of evidence supporting their use, platelet transfusions are still recommended in ophthalmologic and neurosurgical procedures when the platelet count is less than 100,000/ μL .

The PT and aPTT are variations of plasma recalcification times initiated by the addition of a thromboplastic agent. The PT reagent contains thromboplastin and calcium that, when added to plasma, leads to the formation of a fibrin clot. The PT test measures the function of factors I, II, V, VII, and X. Factor VII is part of the extrinsic pathway, and the remaining factors are part of the common pathway. Factor VII has the shortest half-life of the coagulation factors, and its synthesis is vitamin K dependent. The PT test is best suited to detect abnormal coagulation caused by vitamin K deficiencies and warfarin therapy.

Due to variations in thromboplastin activity, it can be difficult to accurately assess the degree of anticoagulation on the basis of PT alone. To account for these variations, the INR is now the method of choice for reporting PT values. The International Sensitivity Index (ISI) is unique to each batch of thromboplastin and is furnished by the manufacturer to the hematology laboratory. Human brain thromboplastin has an ISI of 1, and the optimal reagent has an ISI between 1.3 and 1.5.

The INR is a calculated number derived from the following equation:

$$\text{INR} = (\text{measured PT}/\text{normal PT})^{\text{ISI}}$$

The aPTT reagent contains a phospholipid substitute, activator, and calcium, which in the presence of plasma leads to fibrin clot formation. The aPTT measures function of factors I, II, and V of the common pathway and factors VIII, IX, X, and XII of the intrinsic pathway. Heparin therapy is often monitored by following aPTT values with a therapeutic target range of 1.5 to 2.5 times the control value (approximately 50 to 80 seconds). Low molecular weight heparins are selective Xa inhibitors that may mildly elevate the aPTT, but therapeutic monitoring is not routinely recommended.

The bleeding time is used to evaluate platelet and vascular dysfunction, although not as frequently as in the past. Several standard methods have been described; however, the Ivy bleeding time is most commonly used. It is conducted by placing a sphygmomanometer on the upper arm and inflating it to 40 mmHg, and then a 5-mm stab incision is made on the flexor surface of the forearm. The time is measured to cessation of bleeding, and the upper limit or normal bleeding time with the Ivy test is 7 minutes. A template aids in administering a uniform test and adds to the reproducibility of the results. An abnormal bleeding time suggests platelet dysfunction (intrinsic or drug-induced), vWD, or certain vascular defects. Many laboratories are replacing the template bleeding time with an *in vitro* test in which blood is sucked through a capillary and the platelets adhere to the walls of the capillary and aggregate. The closure time in this system appears to be more reproducible than the bleeding time and also correlates with bleeding in vWD, primary platelet function disorders, and patients who are taking aspirin.

Additional medications may significantly impair hemostatic function, such as antiplatelet agents (clopidogrel and GP IIb/IIIa inhibitors), anticoagulant agents (hirudin, chondroitin sulfate, dermatan sulfate), and thrombolytic agents (streptokinase, tPA). If abnormalities in any of the coagulation studies cannot be explained by known medications, congenital abnormalities of coagulation or comorbid disease should be considered.

Unfortunately, while these conventional tests (PT, aPTT) capture the classic intrinsic and extrinsic coagulation cascade, they do not reflect the complexity of *in vivo* coagulation.⁹² Although they are useful to follow warfarin and heparin therapies, they poorly reflect the status of actively bleeding patients. This is not surprising given that these tests use only plasma and not whole blood to provide their assessment of the patient's clotting status. To better assess the complex and rapidly changing interactions of an actively bleeding patient, many centers have moved to whole blood-viscoelastic testing such as TEG or rotational thromboelastometry (ROTEM). In addition, some centers have demonstrated that the graphical display options allow for more rapid return of results and that these tests are actually less expensive than standard coagulation panels.

TEG was originally described by Hartert in 1948.⁹³ Continuous improvements in this technique have made this test a valuable tool for the medical personnel interested in coagulation. The TEG monitors hemostasis as a dynamic process rather than revealing information of isolated conventional coagulation screens.⁹⁴ The TEG measures the viscoelastic properties of blood as it is induced to clot under a low-shear environment (resembling sluggish venous flow). The patterns of change in shear-elasticity enable the determination of the kinetics of clot formation and growth as well as the strength and stability of the formed clot. The strength and stability provide information about the ability of the clot to perform the work of hemostasis, while the kinetics determines the adequacy of quantitative factors available for clot formation. A sample of celite-activated whole blood is placed into a prewarmed cuvette, and the clotting process is activated with kaolin with standard TEG and kaolin plus tissue factor with rapid TEG. A suspended piston is then lowered into the cuvette that moves in rotation of a 4.5-degree arc backward and forward. The normal clot goes through acceleration and strengthening phase. The fiber strands that interact with activated platelets attach to the surface of the cuvette and the suspended piston. The clot forming in the cuvette transmits its movement onto the suspended piston. A "weak" clot stretches and therefore delays the arc movement of the piston, which is graphically expressed as a narrow TEG. A strong clot, in contrast, will move the piston simultaneously and proportionally to the cuvette's movements, creating a thick TEG. The strength of a clot is graphically represented over time as a characteristic cigar-shape figure (Fig. 4-6).

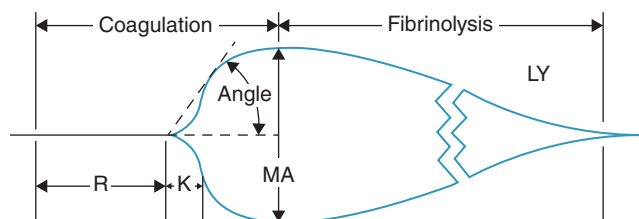


Figure 4-6. Illustration of a thromboelastogram (TEG) tracing. K = clot kinetics; LY = lysis; MA = maximal amplitude; R = reaction time.

Several parameters are generated from the TEG tracing. The r-value (reaction time) represents the time between the start of the assay and initial clot formation. This reflects clotting factor activity and initial fibrin formation and is increased with factor deficiency or severe hemodilution. The k-time (clot kinetics) is the time needed to reach specified clot strength and represents the interactions of clotting factors and platelets. As such, the k-time is prolonged with hypofibrinogenemia and significant factor deficiency. Prolonged r-value and k-time are commonly addressed with plasma transfusions. The alpha or angle (∞) is the slope of the tracing and reflects clot acceleration. The angle reflects the interactions of clotting factors and platelets. The slope is decreased with hypofibrinogenemia and platelet dysfunction. Decreased angles are treated with cryoprecipitate transfusion or fibrinogen administration. The maximal amplitude (mA) is the greatest height of the tracing and represents clot strength. Its height is reduced with dysfunction or deficiencies in platelets or fibrinogen. Decreased mA is addressed with platelet transfusion and, in cases where the angle is also decreased, with cryoprecipitate (or fibrinogen) as well. The G-value is a parametric measure derived from the mA value and reflects overall clot strength or firmness. An increased G-value is associated with hypercoagulability, whereas a decrease is seen with hypocoagulable states. Finally, the LY30 is the amount of lysis occurring in the clot, and the value is the percentage of amplitude reduction at 30 minutes after mA is achieved. The LY30 represents clot stability and when increased fibrinolysis is present.

TEG is the only test measuring all dynamic steps of clot formation until eventual clot lysis or retraction. TEG has also been shown to identify on admission those patients likely to develop thromboembolic complications after injury and postoperatively.⁹⁵⁻⁹⁷

Recent trauma data have shown TEG to be useful in predicting early transfusion of red blood cells, plasma, platelets, and cryoprecipitate.⁹⁸ TEG can also predict the need for life-saving interventions shortly after arrival and to predict 24-hour and 30-day mortality.⁹⁹ Lastly, TEG can be useful to guide administration of TXA to injured patients with hyperfibrinolysis.¹⁰⁰ Our center now uses TEG rather than PT and a PTT to evaluate injured patients in the emergency room.¹⁰¹

EVALUATION OF EXCESSIVE INTRAOPERATIVE OR POSTOPERATIVE BLEEDING

Excessive bleeding during or after a surgical procedure may be the result of ineffective hemostasis, blood transfusion, undetected hemostatic defect, consumptive coagulopathy, and/or fibrinolysis. Excessive bleeding from the operative field unassociated with bleeding from other sites usually suggests inadequate mechanical hemostasis.

Massive blood transfusion is a well-known cause of thrombocytopenia. Bleeding following massive transfusion can occur due to hypothermia, dilutional coagulopathy, platelet dysfunction, fibrinolysis, or hypofibrinogenemia. Another cause of hemostatic failure related to the administration of blood is a hemolytic transfusion reaction. The first sign of a transfusion reaction may be diffuse bleeding. The pathogenesis of this bleeding is thought to be related to the release of ADP from hemolyzed red blood cells, resulting in diffuse platelet aggregation, after which the platelet clumps are removed out of the circulation.

Transfusion purpura occurs when the donor platelets are of the uncommon PIA^1 group. This is an uncommon cause of thrombocytopenia and associated bleeding after transfusion.

The platelets sensitize the recipient, who makes antibody to the foreign platelet antigen. The foreign platelet antigen does not completely disappear from the recipient circulation but attaches to the recipient's own platelets. The antibody then destroys the recipient's own platelets. The resultant thrombocytopenia and bleeding may continue for several weeks. This uncommon cause of thrombocytopenia should be considered if bleeding follows transfusion by 5 or 6 days. Platelet transfusions are of little help in the management of this syndrome because the new donor platelets usually are subject to the binding of antigen and damage from the antibody. Corticosteroids may be of some help in reducing the bleeding tendency. Posttransfusion purpura is self-limited, and the passage of several weeks inevitably leads to subsidence of the problem.

DIC is characterized by systemic activation of the coagulation system, which results in the deposition of fibrin clots and microvascular ischemia and may contribute to the development of multiorgan failure. Consumption and subsequent exhaustion of coagulation proteins and platelets due to the ongoing activation of the coagulation system may induce severe bleeding complications.

Lastly, severe hemorrhagic disorders due to thrombocytopenia have occurred as a result of gram-negative sepsis. Defibrination and hemostatic failure also may occur with meningococemia, *Clostridium perfringens* sepsis, and staphylococcal sepsis. Hemolysis appears to be one mechanism in sepsis leading to defibrination.

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5 chapter

Shock

Brian S. Zuckerbraun, Andrew B. Peitzman, and
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“Shock is the manifestation of the rude unhooking of the machinery of life.”¹

—Samuel V. Gross, 1872

EVOLUTION IN UNDERSTANDING SHOCK

Overview

Shock, at its most rudimentary definition and regardless of the etiology, is the failure to meet the metabolic needs of the cell and the consequences that ensue. The initial cellular injury that occurs is reversible; however, the injury will become irreversible if tissue perfusion is prolonged or severe enough such that, at the cellular level, compensation is no longer possible. Our evolution in the understanding of shock and the disease processes that result in shock made its most significant advances throughout the twentieth century as our appreciation for the physiology and pathophysiology of shock matured. Most notably, this includes the sympathetic and neuroendocrine stress responses on the cardiovascular system. The clinical manifestations of these physiologic responses are most often what lead practitioners to the diagnosis of shock as well as guide the management of patients in shock. However, hemodynamic parameters such as blood pressure and heart rate are relatively insensitive measures of shock, and additional considerations must be used to help aid in early diagnosis and treatment of patients in shock. The general approach to the management of patients in shock has been empiric: assuring a secure airway with adequate ventilation, control of hemorrhage in the bleeding patient, and restoration of vascular volume and tissue perfusion.

Historical Background

Integral to our understanding of shock is the appreciation that our bodies attempt to maintain a state of homeostasis. Claude Bernard suggested in the mid-nineteenth century that the

organism attempts to maintain constancy in the internal environment against external forces that attempt to disrupt the *milieu interieur*.² Walter B. Cannon carried Bernard’s observations further and introduced the term *homeostasis*, emphasizing that an organism’s ability to survive was related to maintenance of homeostasis.³ The failure of physiologic systems to buffer the organism against external forces results in organ and cellular dysfunction, what is clinically recognized as shock. He first described the “fight or flight response,” generated by elevated levels of catecholamines in the bloodstream. Cannon’s observations on the battlefields of World War I led him to propose that the initiation of shock was due to a disturbance of the nervous system that resulted in vasodilation and hypotension. He proposed that secondary shock, with its attendant capillary permeability leak, was caused by a “toxic factor” released from the tissues.

In a series of critical experiments, Alfred Blalock documented that the shock state in hemorrhage was associated with reduced cardiac output due to volume loss, not a “toxic factor.”⁴ In 1934, Blalock proposed four categories of shock: hypovolemic, vasogenic, cardiogenic, and neurogenic. *Hypovolemic shock*, the most common type, results from loss of circulating blood volume. This may result from loss of whole blood (hemorrhagic shock), plasma, interstitial fluid (bowel obstruction), or a combination. *Vasogenic shock* results from decreased resistance within capacitance vessels, usually seen in sepsis. *Neurogenic shock* is a form of vasogenic shock in which spinal cord injury or spinal anesthesia causes vasodilation due to acute loss of sympathetic vascular tone. *Cardiogenic shock* results from failure of the heart as a pump, as in arrhythmias or acute myocardial infarction (MI).

This categorization of shock based on etiology persists today (Table 5-1). In recent clinical practice, further classification has described six types of shock: hypovolemic, septic (vasodilatory), neurogenic, cardiogenic, obstructive, and traumatic shock.

Key Points

- 1▶ Shock is defined as a failure to meet the metabolic demands of cells and tissues and the consequences that ensue.
- 2▶ A central component of shock is decreased tissue perfusion. This may be a direct consequence of the etiology of shock, such as in hypovolemic/hemorrhagic, cardiogenic, or neurogenic etiologies, or may be secondary to elaborated or released molecules or cellular products that result in endothelial/cellular activation, such as in septic shock or traumatic shock.
- 3▶ Physiologic responses to shock are based on a series of afferent (sensing) signals and efferent responses that include neuroendocrine, metabolic, and immune/inflammatory signaling.
- 4▶ The mainstay of treatment of hemorrhagic/hypovolemic shock includes volume resuscitation with blood products. In the case of hemorrhagic shock, timely control of bleeding is essential and influences outcome.
- 5▶ Prevention of hypothermia, acidemia, and coagulopathy is essential in the management of patients in hemorrhagic shock.
- 6▶ The mainstay of treatment of septic shock is fluid resuscitation, initiation of appropriate antibiotic therapy, and control of the source of infection. This includes drainage of infected fluid collections, removal of infected foreign bodies, and débridement of devitalized tissues.
- 7▶ A combination of physiologic parameters and markers of organ perfusion/tissue oxygenation are used to determine if patients are in shock and to follow the efficacy of resuscitation.

Obstructive shock is a form of cardiogenic shock that results from mechanical impediment to circulation leading to depressed cardiac output rather than primary cardiac failure. This includes etiologies such as pulmonary embolism or tension pneumothorax. In *traumatic shock*, soft tissue and bony injury leads to the activation of inflammatory cells and the release of circulating factors, such as cytokines and intracellular molecules that modulate the immune response. Recent investigations have revealed that the inflammatory mediators released in response to tissue injury (damage-associated molecular patterns [DAMPs]) are recognized by many of the same cellular receptors (pattern recognition receptors [PRRs]) and activate similar signaling pathways as do bacterial products elaborated in sepsis (pathogen-associated molecular patterns), such as lipopolysaccharide.⁵ These effects of tissue injury are combined with the effects of hemorrhage, creating a more complex and amplified deviation from homeostasis.

In the mid to later twentieth century, the further development of experimental models contributed significantly to the understanding of the pathophysiology of shock. In 1947, Wiggers developed a sustainable, irreversible model of hemorrhagic shock based on uptake of shed blood into a reservoir to maintain a set level of hypotension.⁶ G. Tom Shires added further understanding of hemorrhagic shock with a series of clinical studies demonstrating that a large extracellular fluid deficit, greater than could be attributed to vascular refilling alone, occurred in severe hemorrhagic shock.^{7,8} The phenomenon of fluid redistribution after major trauma involving blood loss was termed *third spacing* and described the translocation of intravascular volume

into the peritoneum, bowel, burned tissues, or crush injury sites. These seminal studies form the scientific basis for the current treatment of hemorrhagic shock with red blood cells and lactated Ringer's solution or isotonic saline.

As resuscitation strategies evolved and patients survived the initial consequences of hemorrhage, new challenges of sustained shock became apparent. During the Vietnam War, aggressive fluid resuscitation with red blood cells and crystalloid solution or plasma resulted in survival of patients who previously would have succumbed to hemorrhagic shock. Renal failure became a less frequent clinical problem; however, a new disease process, acute fulminant pulmonary failure, appeared as an early cause of death after seemingly successful surgery to control hemorrhage. Initially called *DaNang lung* or *shock lung*, the clinical problem became recognized as acute respiratory distress syndrome (ARDS). This led to new methods of prolonged mechanical ventilation. Our current concept of ARDS is a component in the spectrum of multiple organ system failure.

Studies and clinical observations over the past two decades have extended the early observations of Canon, that "restoration of blood pressure prior to control of active bleeding may result in loss of blood that is sorely needed," and challenged the appropriate endpoints in resuscitation of uncontrolled hemorrhage.⁹ Core principles in the management of the critically ill or injured patient include: (a) definitive control of the airway must be secured, (b) control of active hemorrhage must occur promptly (delay in control of bleeding increases mortality, and recent battlefield data would suggest that in the young and otherwise healthy population commonly injured in combat, control of bleeding is the paramount priority), (c) volume resuscitation with blood products (red blood cells, plasma, and platelets) with limited volume of crystalloid must occur while operative control of bleeding is achieved, (d) unrecognized or inadequately corrected hypoperfusion increases morbidity and mortality (i.e., inadequate resuscitation results in avoidable early deaths from shock), and (e) excessive fluid resuscitation may exacerbate bleeding (i.e., uncontrolled resuscitation is harmful). Thus both inadequate and uncontrolled volume resuscitation is harmful.

Table 5-1

Classification of shock

Hypovolemic
Cardiogenic
Septic (vasogenic)
Neurogenic
Traumatic
Obstructive

Current Definitions and Challenges

A modern definition and approach to shock acknowledges that shock consists of inadequate tissue perfusion marked by

decreased delivery of required metabolic substrates and inadequate removal of cellular waste products. This involves failure of oxidative metabolism that can involve defects of oxygen (O_2) delivery, transport, and/or utilization. Current challenges include moving beyond fluid resuscitation based on endpoints of tissue oxygenation, and using therapeutic strategies at the cellular and molecular level. This approach will help to identify compensated patients or patients early in the course of their disease, initiate appropriate treatment, and allow for continued evaluation for the efficacy of resuscitation and adjuncts.

Current investigations focus on determining the cellular events that often occur in parallel to result in organ dysfunction, shock irreversibility, and death. This chapter will review our current understanding of the pathophysiology and cellular responses of shock states. Current and experimental diagnostic and therapeutic modalities for the different categories of shock are reviewed, with a focus on hemorrhagic/hypovolemic shock and septic shock.

PATHOPHYSIOLOGY OF SHOCK

Regardless of etiology, the initial physiologic responses in shock are driven by tissue hypoperfusion and the developing cellular energy deficit. This imbalance between cellular supply and demand leads to neuroendocrine and inflammatory responses, the magnitude of which is usually proportional to the degree and duration of shock. The specific responses will differ based on the etiology of shock, as certain physiologic responses may be limited by the inciting pathology. For example, the cardiovascular response driven by the sympathetic nervous system is markedly blunted in neurogenic or septic shock. Additionally, decreased perfusion may occur as a consequence of cellular activation and dysfunction, such as in septic shock and to a lesser extent traumatic shock (Fig. 5-1). Many of the organ-specific responses are aimed at maintaining

perfusion in the cerebral and coronary circulation. These are regulated at multiple levels including (a) stretch receptors and baroreceptors in the heart and vasculature (carotid sinus and aortic arch), (b) chemoreceptors, (c) cerebral ischemia responses, (d) release of endogenous vasoconstrictors, (e) shifting of fluid into the intravascular space, and (f) renal reabsorption and conservation of salt and water.

Furthermore, the pathophysiologic responses vary with time and in response to resuscitation. In hemorrhagic shock, the body can compensate for the initial loss of blood volume primarily through the neuroendocrine response to maintain hemodynamics. This represents the *compensated phase* of shock. With continued hypoperfusion, which may be unrecognized, cellular death and injury are ongoing and the *decompensation phase* of shock ensues. Microcirculatory dysfunction, parenchymal tissue damage, and inflammatory cell activation can perpetuate hypoperfusion. Ischemia/reperfusion injury will often exacerbate the initial insult. These effects at the cellular level, if untreated, will lead to compromise of function at the organ system level, thus leading to the “*vicious cycle*” of shock (Fig. 5-2). Persistent hypoperfusion results in further hemodynamic derangements and cardiovascular collapse. This has been termed the *irreversible phase* of shock and can develop quite insidiously and may only be obvious in retrospect. At this point, there has occurred extensive enough parenchymal and microvascular injury such that volume resuscitation fails to reverse the process, leading to death of the patient. In experimental animal models of hemorrhagic shock (modified Wiggers model), this is represented by the “uptake phase” or “compensation endpoint” when shed blood must be returned to the animal to sustain the hypotension at the set level to prevent further hypotension and death.¹⁰ If shed blood volume is slowly returned to maintain the set level of hypotension, eventually the injury progresses to irreversible shock, where further volume will not reverse the process and the animal dies (Fig. 5-3).

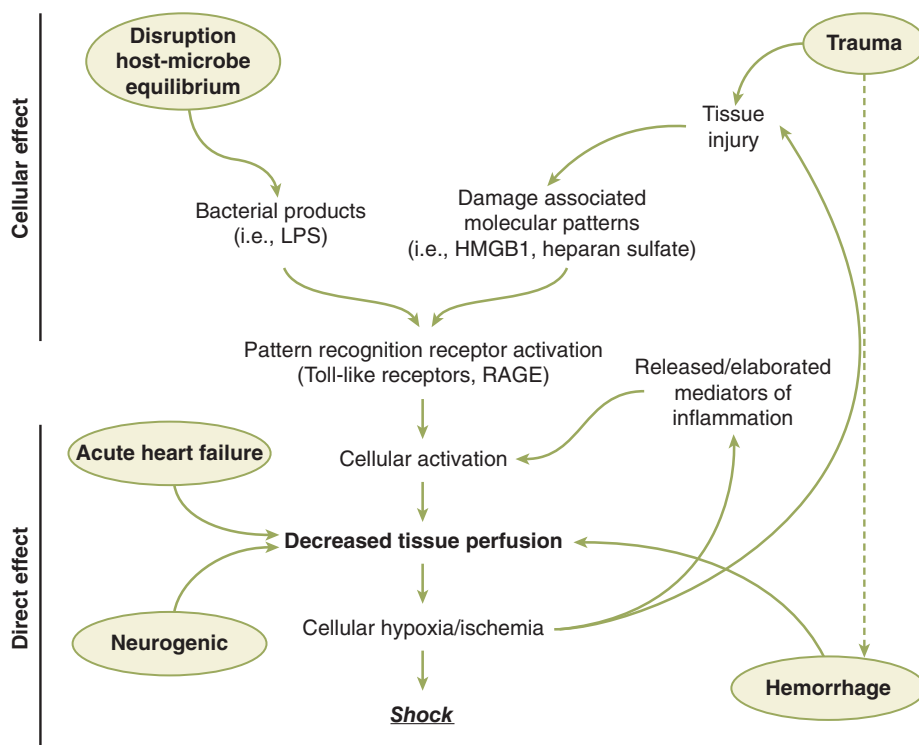


Figure 5-1. Pathways leading to decreased tissue perfusion and shock. Decreased tissue perfusion can result directly from hemorrhage/hypovolemia, cardiac failure, or neurologic injury. Decreased tissue perfusion and cellular injury can then result in immune and inflammatory responses. Alternatively, elaboration of microbial products during infection or release of endogenous cellular products from tissue injury can result in cellular activation to subsequently influence tissue perfusion and the development of shock. HMGB1 = high mobility group box 1; LPS = lipopolysaccharide; RAGE = receptor for advanced glycation end products.

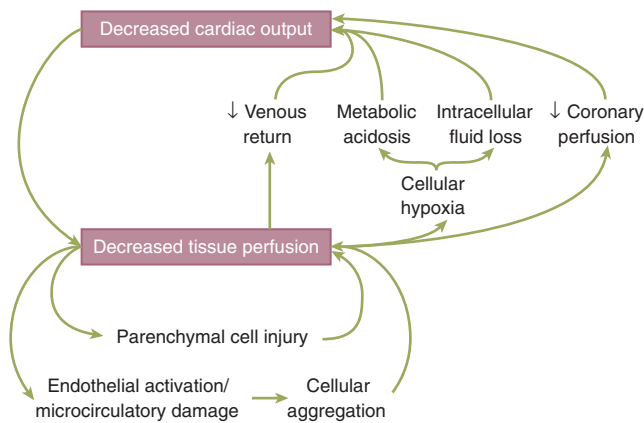


Figure 5-2. The “vicious cycle of shock.” Regardless of the etiology, decreased tissue perfusion and shock results in a feed-forward loop that can exacerbate cellular injury and tissue dysfunction.

Neuroendocrine and Organ-Specific Responses to Hemorrhage

The goal of the neuroendocrine response to hemorrhage is to maintain perfusion to the heart and the brain, even at the expense of other organ systems. Peripheral vasoconstriction occurs, and fluid excretion is inhibited. The mechanisms include autonomic control of peripheral vascular tone and cardiac contractility, hormonal response to stress and volume depletion, and local microcirculatory mechanisms that are organ specific and regulate regional blood flow. The initial stimulus is loss of circulating blood volume in hemorrhagic shock. The magnitude of the neuroendocrine response is based on both the volume of blood lost and the rate at which it is lost.

Afferent Signals

Afferent impulses transmitted from the periphery are processed within the central nervous system (CNS) and activate the reflexive effector responses or efferent impulses. These effector responses are designed to expand plasma volume, maintain

peripheral perfusion and tissue O_2 delivery, and restore homeostasis. The afferent impulses that initiate the body’s intrinsic adaptive responses and converge in the CNS originate from a variety of sources. The initial inciting event usually is loss of circulating blood volume. Other stimuli that can produce the neuroendocrine response include pain, hypoxemia, hypercarbia, acidosis, infection, change in temperature, emotional arousal, or hypoglycemia. The sensation of pain from injured tissue is transmitted via the spinothalamic tracts, resulting in activation of the hypothalamic-pituitary-adrenal axis, as well as activation of the autonomic nervous system (ANS) to induce direct sympathetic stimulation of the adrenal medulla to release catecholamines.

Baroreceptors also are an important afferent pathway in initiation of adaptive responses to shock. Volume receptors, sensitive to changes in both chamber pressure and wall stretch, are present within the atria of the heart. They become activated with low volume hemorrhage or mild reductions in right atrial pressure. Receptors in the aortic arch and carotid bodies respond to alterations in pressure or stretch of the arterial wall, responding to larger reductions in intravascular volume or pressure. These receptors normally inhibit induction of the ANS. When activated, these baroreceptors diminish their output, thus disinhibiting the effect of the ANS. The ANS then increases its output, principally via sympathetic activation at the vasomotor centers of the brain stem, producing centrally mediated constriction of peripheral vessels.

Chemoreceptors in the aorta and carotid bodies are sensitive to changes in O_2 tension, H^+ ion concentration, and carbon dioxide (CO_2) levels. Stimulation of the chemoreceptors results in vasodilation of the coronary arteries, slowing of the heart rate, and vasoconstriction of the splanchnic and skeletal circulation. In addition, a variety of protein and nonprotein mediators are produced at the site of injury as part of the inflammatory response, and they act as afferent impulses to induce a host response. These mediators include histamine, cytokines, eicosanoids, and endothelins, among others that are discussed in greater detail later in this chapter in the Immune and Inflammatory Responses section.

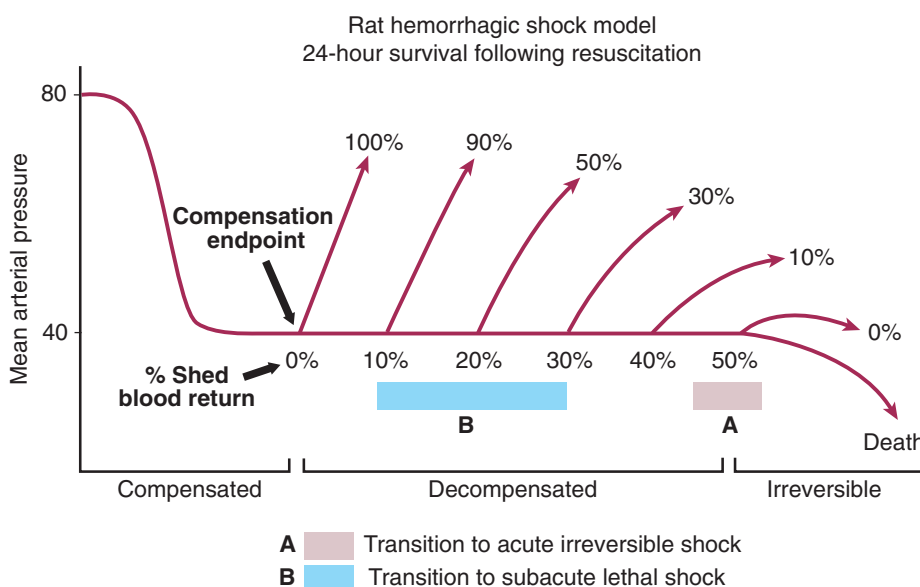


Figure 5-3. Rat model of hemorrhagic shock through the phases of compensation, decompensation, and irreversibility. The percentages shown above the curve represent survival rates. (Adapted with permission from Lippincott Williams & Wilkins/Wolters Kluwer Health: Shah NS, Kelly E, Billiar TR, et al. Utility of clinical parameters of tissue oxygenation in a quantitative model of irreversible hemorrhagic shock. *Shock*. 1998;10:343-346. Copyright © 1998.)

Efferent Signals

Cardiovascular Response. Changes in cardiovascular function are a result of the neuroendocrine response and ANS response to shock, and constitute a prominent feature of both the body's adaptive response mechanism and the clinical signs and symptoms of the patient in shock. Hemorrhage results in diminished venous return to the heart and decreased cardiac output. This is compensated by increased cardiac heart rate and contractility, as well as venous and arterial vasoconstriction. Stimulation of sympathetic fibers innervating the heart leads to activation of β_1 -adrenergic receptors that increase heart rate and contractility in this attempt to increase cardiac output. Increased myocardial O_2 consumption occurs as a result of the increased workload; thus, myocardial O_2 supply must be maintained or myocardial dysfunction will develop. The cardiovascular response in hemorrhage/hypovolemia differs from the responses elicited with the other etiologies of shock. These are compared in Table 5-2.

Direct sympathetic stimulation of the peripheral circulation via the activation of α_1 -adrenergic receptors on arterioles induces vasoconstriction and causes a compensatory increase in systemic vascular resistance and blood pressure. The arterial vasoconstriction is not uniform; marked redistribution of blood flow results. Selective perfusion to tissues occurs due to regional variations in arteriolar resistance, with blood shunted away from less essential organ beds such as the intestine, kidney, and skin. In contrast, the brain and heart have autoregulatory mechanisms that attempt to preserve their blood flow despite a global decrease in cardiac output. Direct sympathetic stimulation also induces constriction of venous vessels, decreasing the capacitance of the circulatory system and accelerating blood return to the central circulation.

Increased sympathetic output induces catecholamine release from the adrenal medulla. Catecholamine levels peak within 24 to 48 hours of injury and then return to baseline. Persistent elevation of catecholamine levels beyond this time suggests ongoing noxious afferent stimuli. The majority of the circulating epinephrine is produced by the adrenal medulla, while norepinephrine is derived from synapses of the sympathetic nervous system. Catecholamine effects on peripheral tissues include stimulation of hepatic glycogenolysis and gluconeogenesis to increase circulating glucose availability to peripheral tissues, an increase in skeletal muscle glycogenolysis, suppression of insulin release, and increased glucagon release.

Hormonal Response. The stress response includes activation of the ANS as discussed earlier in the Afferent Signals section, as well as activation of the hypothalamic-pituitary-adrenal axis. Shock stimulates the hypothalamus to release corticotropin-releasing hormone, which results in the release of adrenocorticotrophic hormone (ACTH) by the pituitary. ACTH subsequently stimulates the adrenal cortex to release cortisol. Cortisol acts synergistically with epinephrine and glucagon to induce a catabolic state. Cortisol stimulates gluconeogenesis and insulin resistance, resulting in hyperglycemia as well as muscle cell protein breakdown and lipolysis to provide substrates for hepatic gluconeogenesis. Cortisol causes retention of sodium and water by the nephrons of the kidney. In the setting of severe hypovolemia, ACTH secretion occurs independently of cortisol negative feedback inhibition.

The renin-angiotensin system is activated in shock. Decreased renal artery perfusion, β -adrenergic stimulation, and increased renal tubular sodium concentration cause the release of renin from the juxtaglomerular cells. Renin catalyzes the conversion of angiotensinogen (produced by the liver) to angiotensin I, which is then converted to angiotensin II by angiotensin-converting enzyme (ACE) produced in the lung. While angiotensin I has no significant functional activity, angiotensin II is a potent vasoconstrictor of both splanchnic and peripheral vascular beds, and also stimulates the secretion of aldosterone, ACTH, and antidiuretic hormone (ADH). Aldosterone, a mineralocorticoid, acts on the nephron to promote reabsorption of sodium and, as a consequence, water. Potassium and hydrogen ions are lost in the urine in exchange for sodium.

The pituitary also releases vasopressin or ADH in response to hypovolemia, changes in circulating blood volume sensed by baroreceptors and left atrial stretch receptors, and increased plasma osmolality detected by hypothalamic osmoreceptors. Epinephrine, angiotensin II, pain, and hyperglycemia increase production of ADH. ADH levels remain elevated for about 1 week after the initial insult, depending on the severity and persistence of the hemodynamic abnormalities. ADH acts on the distal tubule and collecting duct of the nephron to increase water permeability, decrease water and sodium losses, and preserve intravascular volume. Also known as *arginine vasopressin*, ADH acts as a potent mesenteric vasoconstrictor, shunting circulating blood away from the splanchnic organs during hypovolemia.¹¹ This may contribute to intestinal ischemia and predispose to intestinal mucosal barrier dysfunction.

Table 5-2

Hemodynamic responses to different types of shock

TYPE OF SHOCK	CARDIAC INDEX	SVR	VENOUS CAPACITANCE	CVP/PCWP	SVO ₂	CELLULAR/METABOLIC EFFECTS
Hypovolemic	↓	↑	↓	↓	↓	Effect
Septic	↑↑	↓	↑	↑↓	↑↓	Cause
Cardiogenic	↓↓	↑↑	→	↑	↓	Effect
Neurogenic	↑	↓	→	↓	↓	Effect

The hemodynamic responses are indicated by arrows to show an increase (↑), severe increase (↑↑), decrease (↓), severe decrease (↓↓), varied response (↑↓), or little effect (→). CVP = central venous pressure; PCWP = pulmonary capillary wedge pressure; Svo₂ = mixed venous oxygen saturation; SVR = systemic vascular resistance.

in shock states. Vasopressin also increases hepatic gluconeogenesis and increases hepatic glycolysis.

In septic states, endotoxin directly stimulates arginine vasopressin secretion independently of blood pressure, osmotic, or intravascular volume changes. Proinflammatory cytokines also contribute to arginine vasopressin release. Interestingly, patients on chronic therapy with ACE inhibitors are more at risk of developing hypotension and vasodilatory shock with open heart surgery. Low plasma levels of arginine vasopressin were confirmed in these patients.¹²

Circulatory Homeostasis

Preload. At rest, the majority of the blood volume is within the venous system. Venous return to the heart generates ventricular end-diastolic wall tension, a major determinant of cardiac output. Gravitational shifts in blood volume distribution are quickly corrected by alterations in venous capacity. With decreased arteriolar inflow, there is active contraction of the venous smooth muscle and passive elastic recoil in the thin-walled systemic veins. This increases venous return to the heart, thus maintaining ventricular filling.

Most alterations in cardiac output in the normal heart are related to changes in preload. Increases in sympathetic tone have a minor effect on skeletal muscle beds but produce a dramatic reduction in splanchnic blood volume, which normally holds 20% of the blood volume.

The normal circulating blood volume is maintained within narrow limits by the kidney's ability to manage salt and water balance with external losses via systemic and local hemodynamic changes and hormonal effects of renin, angiotensin, and ADH. These relatively slow responses maintain preload by altering circulating blood volume. Acute responses to intravascular volume include changes in venous tone, systemic vascular resistance, and intrathoracic pressure, with the slower hormonal changes less important in the early response to volume loss. Furthermore, the net effect of preload on cardiac output is influenced by cardiac determinants of ventricular function, which include coordinated atrial activity and tachycardia.

Ventricular Contraction. The Frank-Starling curve describes the force of ventricular contraction as a function of its preload. This relationship is based on force of contraction being determined by initial muscle length. Intrinsic cardiac disease will shift the Frank-Starling curve and alter mechanical performance of the heart. In addition, cardiac dysfunction has been demonstrated experimentally in burns and in hemorrhagic, traumatic, and septic shock.

Afterload. Afterload is the force that resists myocardial work during contraction. Arterial pressure is the major component of afterload influencing the ejection fraction. This vascular resistance is determined by precapillary smooth muscle sphincters. Blood viscosity also will increase vascular resistance. As afterload increases in the normal heart, stroke volume can be maintained by increases in preload. In shock, with decreased circulating volume and therefore diminished preload, this compensatory mechanism to sustain cardiac output is impeded. The stress response with acute release of catecholamines and sympathetic nerve activity in the heart increases contractility and heart rate.

Microcirculation. The microvascular circulation plays an integral role in regulating cellular perfusion and is significantly influenced in response to shock. The microvascular bed is

innervated by the sympathetic nervous system and has a profound effect on the larger arterioles. Following hemorrhage, larger arterioles vasoconstrict; however, in the setting of sepsis or neurogenic shock, these vessels vasodilate. Additionally, a host of other vasoactive proteins, including vasopressin, angiotensin II, and endothelin-1, also lead to vasoconstriction to limit organ perfusion to organs such as skin, skeletal muscle, kidneys, and the gastrointestinal (GI) tract to preserve perfusion of the myocardium and CNS.

Flow in the capillary bed is heterogeneous in shock states, which likely is secondary to multiple local mechanisms, including endothelial cell swelling, dysfunction, and activation marked by the recruitment of leukocytes and platelets.¹³ Together, these mechanisms lead to diminished capillary perfusion that may persist after resuscitation. In hemorrhagic shock, correction of hemodynamic parameters and restoration of O₂ delivery generally lead to restoration of tissue O₂ consumption and tissue O₂ levels. In contrast, regional tissue dysoxia often persists in sepsis, despite similar restoration of hemodynamics and O₂ delivery. Whether this defect in O₂ extraction in sepsis is the result of heterogeneous impairment of the microcirculation (intraparenchymal shunting) or impaired tissue parenchymal cell oxidative phosphorylation and O₂ consumption by the mitochondria is not resolved.¹⁴ Interesting data suggest that in sepsis the response to limit O₂ consumption by the tissue parenchymal cells is an adaptive response to the inflammatory signaling and decreased perfusion.¹⁵

An additional pathophysiologic response of the microcirculation to shock is failure of the integrity of the endothelium of the microcirculation and development of capillary leak, intracellular swelling, and the development of an extracellular fluid deficit. Seminal work by Shires helped to define this phenomenon.^{8,16} There is decreased capillary hydrostatic pressure secondary to changes in blood flow and increased cellular uptake of fluid. The result is a loss of extracellular fluid volume. The cause of intracellular swelling is multifactorial, but dysfunction of energy-dependent mechanisms, such as active transport by the sodium-potassium pump, contributes to loss of membrane integrity.

Capillary dysfunction also occurs secondary to activation of endothelial cells by circulating inflammatory mediators generated in septic or traumatic shock. This exacerbates endothelial cell swelling and capillary leak, as well as increases leukocyte adherence. This results in capillary occlusion, which may persist after resuscitation, and is termed *no-reflow*. Further ischemic injury ensues as well as release of inflammatory cytokines to compound tissue injury. Experimental models have shown that neutrophil depletion in animals subjected to hemorrhagic shock produces fewer capillaries with no-reflow and lower mortality.¹³

METABOLIC EFFECTS

Cellular metabolism is based primarily on the hydrolysis of adenosine triphosphate (ATP). The splitting of the phosphoanhydride bond of the terminal or γ -phosphate from ATP is the source of energy for most processes within the cell under normal conditions. The majority of ATP is generated in our bodies through aerobic metabolism in the process of oxidative phosphorylation in the mitochondria. This process is dependent on the availability of O₂ as a final electron acceptor in the electron transport chain. As O₂ tension within a cell decreases, there is a decrease in oxidative phosphorylation, and the generation

of ATP slows. When O_2 delivery is so severely impaired such that oxidative phosphorylation cannot be sustained, the state is termed *dysoxia*.¹⁷ When oxidative phosphorylation is insufficient, the cells shift to anaerobic metabolism and glycolysis to generate ATP. This occurs via the breakdown of cellular glycogen stores to pyruvate. Although glycolysis is a rapid process, it is not efficient, allowing for the production of only 2 mol of ATP from 1 mol of glucose. This is compared to complete oxidation of 1 mol of glucose that produces 38 mol of ATP. Additionally, under hypoxic conditions in anaerobic metabolism, pyruvate is converted into lactate, leading to an intracellular metabolic acidosis.

There are numerous consequences secondary to these metabolic changes. The depletion of ATP potentially influences all ATP-dependent cellular processes. This includes maintenance of cellular membrane potential, synthesis of enzymes and proteins, cell signaling, and DNA repair mechanisms. Decreased intracellular pH also influences vital cellular functions such as normal enzyme activity, cell membrane ion exchange, and cellular metabolic signaling.¹⁸ These changes also will lead to changes in gene expression within the cell. Furthermore, acidosis leads to changes in calcium metabolism and calcium signaling. Compounded, these changes may lead to irreversible cell injury and death.

Epinephrine and norepinephrine have a profound impact on cellular metabolism. Hepatic glycogenolysis, gluconeogenesis, ketogenesis, skeletal muscle protein breakdown, and adipose tissue lipolysis are increased by catecholamines. Cortisol, glucagon, and ADH also contribute to the catabolism during shock. Epinephrine induces further release of glucagon, while inhibiting the pancreatic β -cell release of insulin. The result is a catabolic state with glucose mobilization, hyperglycemia, protein breakdown, negative nitrogen balance, lipolysis, and insulin resistance during shock and injury. The relative underuse of glucose by peripheral tissues preserves it for the glucose-dependent organs such as the heart and brain.

Cellular Hypoperfusion

Hypoperfused cells and tissues experience what has been termed *oxygen debt*, a concept first proposed by Crowell in 1961.¹⁹ The O_2 debt is the deficit in tissue oxygenation over time that occurs during shock. When O_2 delivery is limited, O_2 consumption can be inadequate to match the metabolic needs of cellular respiration, creating a deficit in O_2 requirements at the cellular level. The measurement of O_2 deficit uses calculation of the difference between the estimated O_2 demand and the actual value obtained for O_2 consumption. Under normal circumstances, cells can “repay” the O_2 debt during reperfusion. The magnitude of the O_2 debt correlates with the severity and duration of hypoperfusion. Surrogate values for measuring O_2 debt include base deficit and lactate levels and are discussed later in the Hypovolemic/Hemorrhagic section.

In addition to induction of changes in cellular metabolic pathways, shock also induces changes in cellular gene expression. The DNA binding activity of a number of nuclear transcription factors is altered by hypoxia and the production of O_2 radicals or nitrogen radicals that are produced at the cellular level by shock. Expression of other gene products such as heat shock proteins, vascular endothelial growth factor, inducible nitric oxide synthase (iNOS), heme oxygenase-1, and cytokines also are clearly increased by shock.²⁰ Many of these shock-induced gene products, such as cytokines, have the ability to

subsequently alter gene expression in specific target cells and tissues. The involvement of multiple pathways emphasizes the complex, integrated, and overlapping nature of the response to shock.

IMMUNE AND INFLAMMATORY RESPONSES

The inflammatory and immune responses are a complex set of interactions between circulating soluble factors and cells that can arise in response to trauma, infection, ischemia, toxic, or autoimmune stimuli.²⁰ The processes are well regulated and can be conceptualized as an ongoing surveillance and response system that undergoes a coordinated escalation following injury to heal disrupted tissue or restore host-microbe equilibrium, as well as active suppression back to baseline levels. Failure to adequately control the activation, escalation, or suppression of the inflammatory response can lead to systemic inflammatory response syndrome and potentiate multiple organ failure.

Both the innate and adaptive branches of the immune system work in concert to rapidly respond in a specific and effective manner to challenges that threaten an organism’s well-being. Each arm of the immune system has its own set of functions, defined primarily by distinct classes of effector cells and their unique cell membrane receptor families. Alterations in the activity of the innate host immune system can be responsible for both the development of shock (i.e., septic shock following severe infection and traumatic shock following tissue injury with hemorrhage) and the pathophysiologic sequelae of shock such as the proinflammatory changes seen following hypoperfusion (see Fig. 5-1). When the predominantly paracrine mediators gain access to the systemic circulation, they can induce a variety of metabolic changes that are collectively referred to as the *host inflammatory response*. Understanding of the intricate, redundant, and interrelated pathways that comprise the inflammatory response to shock continues to expand. Despite limited understanding of how our current therapeutic interventions impact the host response to illness, inappropriate or excessive inflammation appears to be an essential event in the development of ARDS, multiple organ dysfunction syndrome (MODS), and posttraumatic immunosuppression that can prolong recovery.²¹

Following direct tissue injury or infection, there are several mechanisms that lead to the activation of the active inflammatory and immune responses. These include release of bioactive peptides by neurons in response to pain and the release of intracellular molecules by broken cells, such as heat shock proteins, mitochondrial products, heparan sulfate, high mobility group box 1, and RNA. Only recently has it been realized that the release of intracellular products from damaged and injured cells can have paracrine and endocrine-like effects on distant tissues to activate the inflammatory and immune responses.²² This hypothesis, which was first proposed by Matzinger, is known as *danger signaling*. Under this novel paradigm of immune function, endogenous molecules are capable of signaling the presence of danger to surrounding cells and tissues. These molecules that are released from cells are known as *damage-associated molecular patterns (DAMPs)* (Table 5-3). DAMPs are recognized by cell surface receptors to effect intracellular signaling that primes and amplifies the immune response. These receptors are known as *pattern recognition receptors (PRRs)* and include the Toll-like receptors (TLRs) and the receptor for advanced glycation end products.

Table 5-3

Endogenous damage-associated molecular pattern molecules

Mitochondrial DNA
Hyaluronan oligomers
Heparan sulfate
Extra domain A of fibronectin
Heat shock proteins 60, 70, Gp96
Surfactant Protein A
β-Defensin 2
Fibrinogen
Biglycan
High mobility group box 1
Uric acid
Interleukin-1α
S-100s
Nucleolin

Interestingly, TLRs and PRRs were first recognized for their role in signaling as part of the immune response to the entry of microbes and their secreted products into a normally sterile environment. These bacterial products, including lipopolysaccharide, are known as *pathogen-associated molecular patterns*. The salutary consequences of PRR activation most likely relate to the initiation of the repair process and the mobilization of antimicrobial defenses at the site of tissue disruption. However, in the setting of excessive tissue damage, the inflammation itself may lead to further tissue damage, amplifying the response both at the local and systemic level.²⁰ PRR activation leads to intracellular signaling and release of cellular products including cytokines (Fig. 5-4).

Before the recruitment of leukocytes into sites of injury, tissue-based macrophages or mast cells act as sentinel responders, releasing histamines, eicosanoids, tryptases, and cytokines (Fig. 5-5). Together these signals amplify the immune response

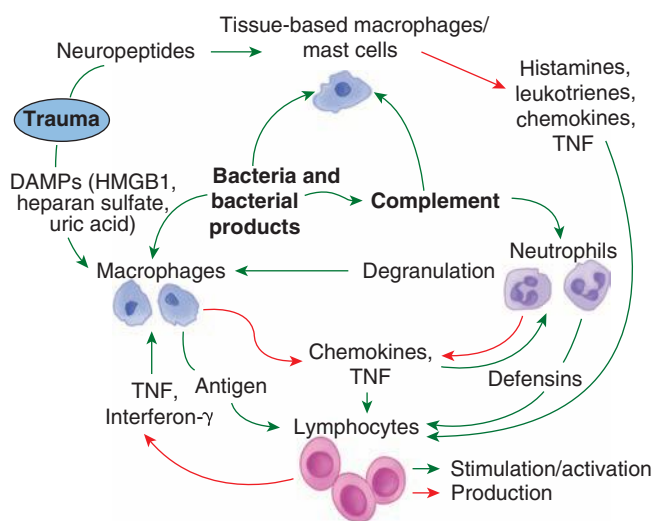


Figure 5-4. A schema of information flow between immune cells in early inflammation following tissue injury and infection. Cells require multiple inputs and stimuli before activation of a full response. DAMPs = damage-associated molecular patterns; HMGB1 = high mobility group box 1; TNF = tumor necrosis factor.

by further activation of neurons and mast cells, as well as increasing the expression of adhesion molecules on the endothelium. Furthermore, these mediators cause leukocytes to release platelet-activating factor, further increasing the stickiness of the endothelium. Additionally, the coagulation and kinin cascades impact the interaction of endothelium and leukocytes.

Cytokines/Chemokines

The immune response to shock encompasses the elaboration of mediators with both proinflammatory and anti-inflammatory properties (Table 5-4). Furthermore, new mediators, new relationships between mediators, and new functions of known mediators are continually being identified. As new pathways are uncovered, understanding of the immune response to injury and the potential for therapeutic intervention by manipulating the immune response following shock will expand. What seems clear at present, however, is that the innate immune response can help restore homeostasis, or if it is excessive, promote cellular and organ dysfunction.

Multiple mediators have been implicated in the host immune response to shock. It is likely that some of the most important mediators have yet to be discovered, and the roles of many known mediators have not been defined. A comprehensive description of all of the mediators and their complex interactions is beyond the scope of this chapter. For a general overview, a brief description of the more extensively studied mediators, and some of the known effects of these substances, see the discussion below. A more comprehensive review can be found in Chap. 2.

Tumor necrosis factor alpha (TNF-α) was one of the first cytokines to be described and is one of the earliest cytokines released in response to injurious stimuli. Monocytes, macrophages, and T cells release this potent proinflammatory cytokine. TNF-α levels peak within 90 minutes of stimulation and return frequently to baseline levels within 4 hours. Release of TNF-α may be induced by bacteria or endotoxin and leads to the development of shock and hypoperfusion, most commonly observed in septic shock. Production of TNF-α also may be induced following other insults, such as hemorrhage and ischemia. TNF-α levels correlate with mortality in animal models of hemorrhage.²³ In contrast, the increase in serum TNF-α levels reported in trauma patients is far less than that seen in septic patients.²⁴ Once released, TNF-α can produce peripheral vasodilation, activate the release of other cytokines, induce procoagulant activity, and stimulate a wide array of cellular metabolic changes. During the stress response, TNF-α contributes to the muscle protein breakdown and cachexia.

Interleukin-1 (IL-1) has actions similar to those of TNF-α. IL-1 has a very short half-life (6 min) and primarily acts in a paracrine fashion to modulate local cellular responses. Systemically, IL-1 produces a febrile response to injury by activating prostaglandins in the posterior hypothalamus, and causes anorexia by activating the satiety center. This cytokine also augments the secretion of ACTH, glucocorticoids, and β-endorphins. In conjunction with TNF-α, IL-1 can stimulate the release of other cytokines such as IL-2, IL-4, IL-6, IL-8, granulocyte-macrophage colony-stimulating factor, and interferon-γ.

IL-2 is produced by activated T cells in response to a variety of stimuli and activates other lymphocyte subpopulations and natural killer cells. The lack of clarity regarding the role of IL-2 in the response to shock is intimately associated

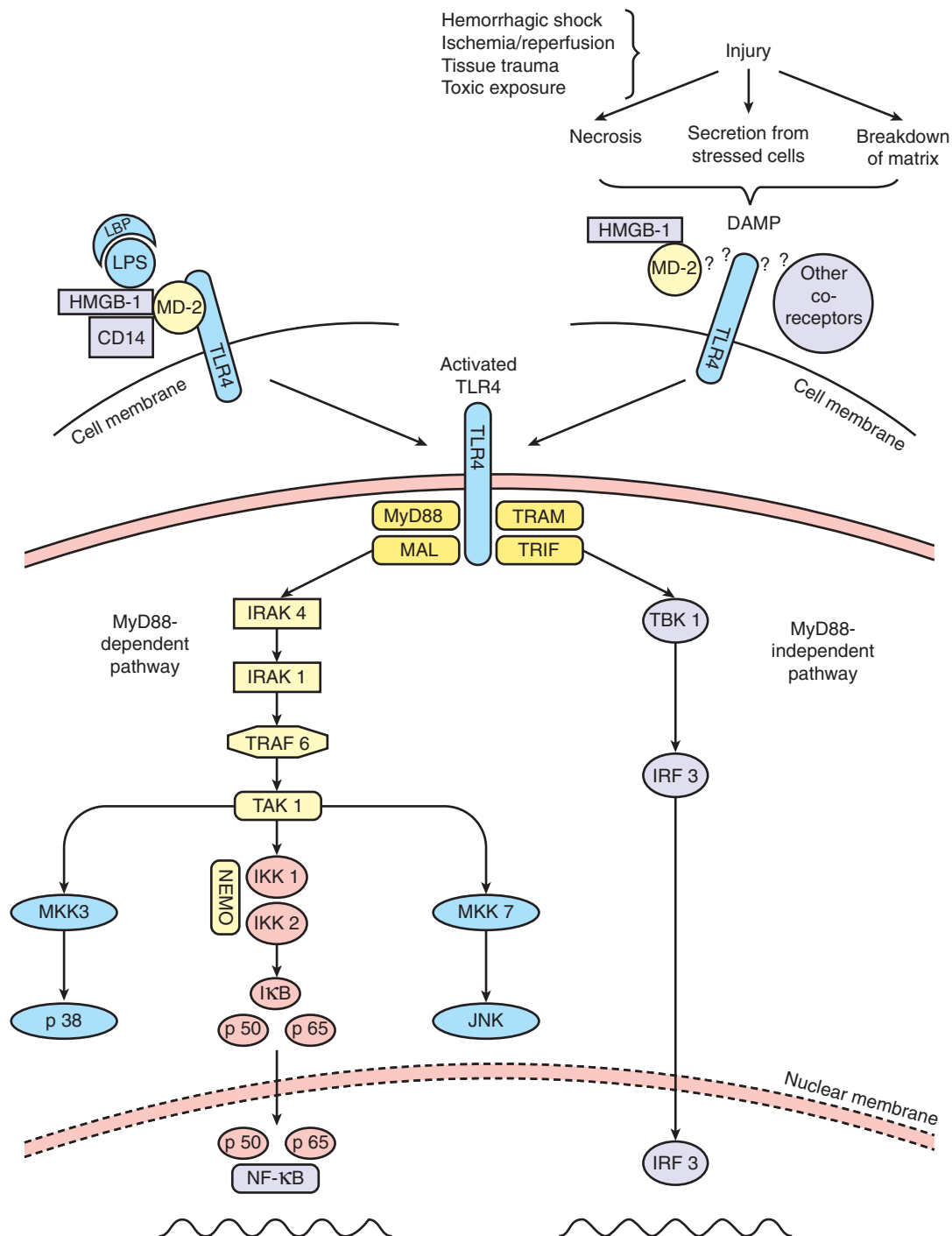


Figure 5-5. Signaling via the pattern recognition receptor TLR4. LPS signaling via TLR4 requires the cofactors LPS binding protein (LBP), MD-2, and CD14. Endogenous danger signals released from a variety of sources also signal in a TLR4-dependent fashion, although it is as yet unknown what cofactors may be required for this activity. Once TLR4 is activated, an intracellular signaling cascade is initiated that involves both a MyD88-dependent and independent pathway. DAMP = damage-associated molecular pattern; LPS = lipopolysaccharide; MD-2 = myeloid differentiation factor-2; MyD88 = myeloid differentiation primary response gene 88; NF-κB = nuclear factor-κB; TLR4 = Toll-like receptor-4. (Reproduced with permission from Mollen KP, Anand RJ, Tsung A, et al.⁸³ Emerging paradigm: toll-like receptor 4-sentinel for the detection of tissue damage. *Shock*. 2006;26:430–437.)

with that of understanding immune function after injury. Some investigators have postulated that increased IL-2 secretion promotes shock-induced tissue injury and the development of shock. Others have demonstrated that depressed IL-2 production is associated with, and perhaps contributes to, the depression in immune function after hemorrhage that may

increase the susceptibility of patients who develop shock to suffer infections.^{25,26} It has been postulated that overly exuberant proinflammatory activation promotes tissue injury, organ dysfunction, and the subsequent immune dysfunction/suppression that may be evident later.²¹ Emphasizing the importance of temporal changes in the production of mediators, both the

Table 5-4

Inflammatory mediators of shock

PROINFLAMMATORY	ANTI-INFLAMMATORY
Interleukin-1 α/β	Interleukin-4
Interleukin-2	Interleukin-10
Interleukin-6	Interleukin-13
Interleukin-8	Prostaglandin E ₂
Interferon	TGF β
TNF	
PAF	

PAF = platelet activating factor; TGF β = transforming growth factor beta; TNF = tumor necrosis factor.

initial excessive production of IL-2 and later depressed IL-2 production are probably important in the progression of shock.

IL-6 is elevated in response to hemorrhagic shock, major operative procedures, or trauma. Elevated IL-6 levels correlate with mortality in shock states. IL-6 contributes to lung, liver, and gut injury after hemorrhagic shock.²⁷ Thus, IL-6 may play a role in the development of diffuse alveolar damage and ARDS. IL-6 and IL-1 are mediators of the hepatic acute phase response to injury; enhance the expression and activity of complement, C-reactive protein, fibrinogen, haptoglobin, amyloid A, and α_1 -antitrypsin; and promote neutrophil activation.²⁸

IL-10 is considered an anti-inflammatory cytokine that may have immunosuppressive properties. Its production is increased after shock and trauma, and it has been associated with depressed immune function clinically, as well as an increased susceptibility to infection.²⁹ IL-10 is secreted by T cells, monocytes, and macrophages, and inhibits proinflammatory cytokine secretion, O₂ radical production by phagocytes, adhesion molecule expression, and lymphocyte activation.^{29,30} Administration of IL-10 depresses cytokine production and improves some aspects of immune function in experimental models of shock and sepsis.^{31,32}

Recent studies point to the importance of chemokines, a specific set of cytokines, that have the ability to induce chemotaxis of leukocytes. Chemokines bind to specific chemokine receptors and transduce chemotactic signals to leukocytes. The significance of this large family of chemoattractant cytokines in immunology is difficult to understate, as almost every facet of the immune system is influenced by chemokines, including immune system development, immune surveillance, immune priming, effector responses, and immune regulation.³³

Complement

The complement cascade can be activated by injury, shock, and severe infection, and contributes to host defense and pro-inflammatory activation. Significant complement consumption occurs after hemorrhagic shock.³⁴ In trauma patients, the degree of complement activation is proportional to the magnitude of injury and may serve as a marker for severity of injury. Patients in septic shock also demonstrate activation of the complement pathway, with elevations of the activated complement proteins C3a and C5a. Activation of the complement cascade can contribute to the development of organ dysfunction. Activated complement factors C3a, C4a, and

C5a are potent mediators of increased vascular permeability, smooth muscle cell contraction, histamine and arachidonic acid by-product release, and adherence of neutrophils to vascular endothelium. Activated complement acts synergistically with endotoxin to induce the release of TNF- α and IL-1. The development of ARDS and MODS in trauma patients correlates with the intensity of complement activation.³⁵ Complement and neutrophil activation may correlate with mortality in multiply injured patients.

Neutrophils

Neutrophil activation is an early event in the upregulation of the inflammatory response; neutrophils are the first cells to be recruited to the site of injury. Polymorphonuclear leukocytes (PMNs) remove infectious agents, foreign substances that have penetrated host barrier defenses, and nonviable tissue through phagocytosis. However, activated PMNs and their products may also produce cell injury and organ dysfunction. Activated PMNs generate and release a number of substances that may induce cell or tissue injury, such as reactive O₂ species, lipid-peroxidation products, proteolytic enzymes (elastase, cathepsin G), and vasoactive mediators (leukotrienes, eicosanoids, and platelet-activating factor). Oxygen free radicals, such as superoxide anion, hydrogen peroxide, and hydroxyl radical, are released and induce lipid peroxidation, inactivate enzymes, and consume antioxidants (such as glutathione and tocopherol). Ischemia-reperfusion activates PMNs and causes PMN-induced organ injury. In animal models of hemorrhagic shock, activation of PMNs correlates with irreversibility of shock and mortality, and neutrophil depletion prevents the pathophysiologic sequelae of hemorrhagic and septic shock. Human data corroborate the activation of neutrophils in trauma and shock and suggest a role in the development of MODS.³⁶ Plasma markers of PMN activation, such as elastase, correlate with severity of injury in humans.

Interactions between endothelial cells and leukocytes are important in the inflammatory process. The vascular endothelium contributes to regulation of blood flow, leukocyte adherence, and the coagulation cascade. Extracellular ligands such as intercellular adhesion molecules, vascular cell adhesion molecules, and the selectins (E-selectin, P-selectin) are expressed on the surface of endothelial cells and are responsible for leukocyte adhesion to the endothelium. This interaction allows activated neutrophils to migrate into the tissues to combat infection, but also can lead to PMN-mediated cytotoxicity and microvascular and tissue injury.

Cell Signaling

A host of cellular changes occur following shock. Although many of the intracellular and intercellular pathways that are important in shock are being elucidated, undoubtedly there are many more that have yet to be identified. Many of the mediators produced during shock interact with cell surface receptors on target cells to alter target cell metabolism. These signaling pathways may be altered by changes in cellular oxygenation, redox state, high-energy phosphate concentration, gene expression, or intracellular electrolyte concentration induced by shock. Cells communicate with their external environment through the use of cell surface membrane receptors, which, once bound by a ligand, transmit their information to the interior of the cell through a variety of signaling cascades. These signaling pathways may subsequently alter the activity of specific enzymes or the expression or breakdown of important proteins or affect

intracellular energy metabolism. Intracellular calcium (Ca^{2+}) homeostasis and regulation represent one such pathway. Intracellular Ca^{2+} concentrations regulate many aspects of cellular metabolism; many important enzyme systems require Ca^{2+} for full activity. Profound changes in intracellular Ca^{2+} levels and Ca^{2+} transport are seen in models of shock.³⁷ Alterations in Ca^{2+} regulation may lead to direct cell injury, changes in transcription factor activation, alterations in the expression of genes important in homeostasis, and the modulation of the activation of cells by other shock-induced hormones or mediators.^{38,39}

A proximal portion of the intracellular signaling cascade consists of a series of kinases that transmit and amplify the signal through the phosphorylation of target proteins. The O_2 radicals produced during shock and the intracellular redox state are known to influence the activity of components of this cascade, such as protein tyrosine kinases, mitogen activated kinases, and protein kinase C.⁴⁰⁻⁴² Either through changes in these signaling pathways, changes in the activation of enzyme systems through Ca^{2+} -mediated events, or direct conformational changes to oxygen-sensitive proteins, O_2 radicals also regulate the activity of a number of transcription factors that are important in gene expression, such as nuclear factor- κB , APETALA1, and hypoxia-inducible factor 1.^{43,44} It is therefore becoming increasingly clear that oxidant-mediated direct cell injury is merely one consequence of the production of O_2 radicals during shock.

The study of the effects of shock on the regulation of gene expression as an important biologic effect was stimulated by the work of Buchman and colleagues.⁴⁵ The effects of shock on the expression and regulation of numerous genes and gene products has been studied in both experimental animal models and human patients. These studies include investigations into single genes of interest as well as large-scale genomic and proteomic analysis.⁴⁶⁻⁴⁸ Changes in gene expression are critical for adaptive and survival cell signaling. Polymorphisms in gene promoters that lead to a differential level of expression of gene products are also likely to contribute significantly to varied responses to similar insults.^{49,50} In a recent study, the genetic responses to traumatic injury in humans or endotoxin delivery to healthy human volunteers demonstrated that severe stresses produce a global reprioritization affecting >80% of the cellular functions and pathways.⁵¹ The similarities in genomic responses between different injuries revealed a fundamental human response to stressors involving dysregulated immune responses (Fig. 5-6). Furthermore, in the traumatic injury patients, complications like nosocomial infections and organ failure were not associated with any genomic evidence of a second hit and differed only in the magnitude and duration of this genomic reprioritization.

FORMS OF SHOCK

Hypovolemic/Hemorrhagic

The most common cause of shock in the surgical or trauma patient is loss of circulating volume from hemorrhage. Acute blood loss results in reflexive decreased baroreceptor stimulation from stretch receptors in the large arteries, resulting in decreased inhibition of vasoconstrictor centers in the brain stem, increased chemoreceptor stimulation of vasomotor centers, and diminished output from atrial stretch receptors. These changes increase vasoconstriction and peripheral arterial resistance. Hypovolemia also induces sympathetic stimulation, leading to epinephrine and norepinephrine release, activation of the renin-angiotensin cascade, and increased vasopressin release. Peripheral vasoconstriction

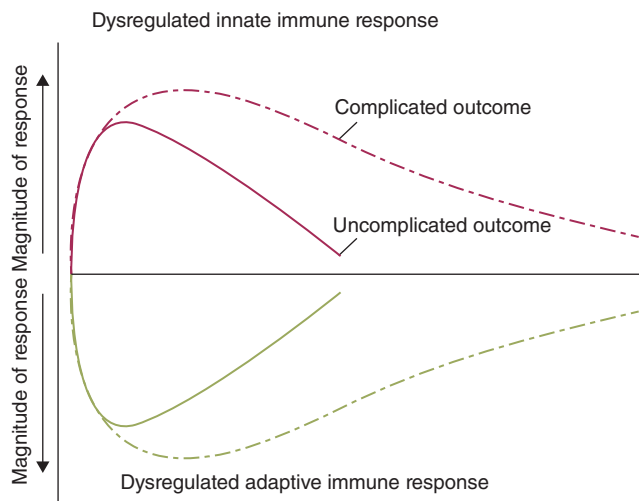


Figure 5-6. The concurrent dysregulated innate immune responses that promote inflammation and dysregulated adaptive immune responses that result in immunosuppression occur in patients following traumatic injury. However, these genetic responses can result in complicated outcomes in trauma patients if the magnitude or duration of these responses is pronounced. (Reproduced with permission from Xiao W, Mindrinos MN, Seok J, et al. A genomic storm in critically injured humans. *J Exp Med*. 2011;208:2581–2590. © 2011 Xiao et al. doi: 10.1084/jem.20111354.)

is prominent, while lack of sympathetic effects on cerebral and coronary vessels and local autoregulation promote maintenance of cardiac and CNS blood flow.

Diagnosis. Treatment of shock is initially empiric. A secure airway must be confirmed or established and volume infusion initiated while the search for the cause of the hypotension is pursued. Shock in a trauma patient or postoperative patient should be presumed to be due to hemorrhage until proven otherwise. The clinical signs of shock may be evidenced by agitation, cool clammy extremities, tachycardia, weak or absent peripheral pulses, and hypotension. Such apparent clinical shock results from at least 25% to 30% loss of the blood volume. However, substantial volumes of blood may be lost before the classic clinical manifestations of shock are evident. Thus, when a patient is significantly tachycardic or hypotensive, this represents both significant blood loss and physiologic decompensation. The clinical and physiologic response to hemorrhage has been classified according to the magnitude of volume loss. Loss of up to 15% of the circulating volume (700–750 mL for a 70-kg patient) may produce little in terms of obvious symptoms, while loss of up to 30% of the circulating volume (1.5 L) may result in mild tachycardia, tachypnea, and anxiety. Hypotension, marked tachycardia (i.e., pulse greater than 110–120 beats per minute [bpm]), and confusion may not be evident until more than 30% of the blood volume has been lost; loss of 40% of circulating volume (2 L) is immediately life threatening and generally requires operative control of bleeding (Table 5-5). Young healthy patients with vigorous compensatory mechanisms may tolerate larger volumes of blood loss while manifesting fewer clinical signs despite the presence of significant peripheral hypoperfusion. These patients may maintain a near-normal blood pressure until a precipitous cardiovascular collapse occurs. Elderly patients may be taking medications that either promote bleeding (e.g., warfarin or aspirin) or mask the compensatory responses

Table 5-5

Classification of hemorrhage

PARAMETER	CLASS			
	I	II	III	IV
Blood loss (mL)	<750	750–1500	1500–2000	>2000
Blood loss (%)	<15	15–30	30–40	>40
Heart rate (bpm)	<100	>100	>120	>140
Blood pressure	Normal	Orthostatic	Hypotension	Severe hypotension
CNS symptoms	Normal	Anxious	Confused	Obtunded

bpm = beats per minute; CNS = central nervous system.

to bleeding (e.g., β -blockers). In addition, atherosclerotic vascular disease, diminishing cardiac compliance with age, inability to elevate heart rate or cardiac contractility in response to hemorrhage, and overall decline in physiologic reserve decrease the elderly patient's ability to tolerate hemorrhage. Recent data in trauma patients suggest that a systolic blood pressure (SBP) of less than 110 mmHg is a clinically relevant definition of hypotension and hypoperfusion based on an increasing rate of mortality below this pressure (Fig. 5-7).⁵²

In addressing the sensitivity of vital signs and identifying major thoracoabdominal hemorrhage, a study retrospectively identified patients with injury to the trunk and an abbreviated injury score of 3 or greater who required immediate surgical intervention and transfusion of at least 5 units of blood within the first 24 hours. Ninety-five percent of patients had a heart rate greater than 80 bpm at some point during their postinjury course. However, only 59% of patients achieved a heart rate greater than 120 bpm. Ninety-nine percent of all patients had a recorded blood pressure of less than 120 mmHg at some point. Ninety-three percent of all patients had a recorded SBP of less than 100 mmHg.⁵³ A more recent study corroborated that tachycardia was not a reliable sign of hemorrhage following trauma and was present in only 65% of hypotensive patients.⁵⁴

Serum lactate and base deficit are measurements that are helpful to both estimate and monitor the extent of bleeding and shock. The amount of lactate that is produced by anaerobic respiration is an indirect marker of tissue hypoperfusion, cellular O₂ debt, and the severity of hemorrhagic shock. Several studies have demonstrated that the initial serum lactate and serial lactate levels are reliable predictors of morbidity and mortality

with hemorrhage following trauma (Fig. 5-8).⁵⁵ Similarly, base deficit values derived from arterial blood gas analysis provide clinicians with an indirect estimation of tissue acidosis from hypoperfusion. Davis and colleagues stratified the extent of base deficit into mild (–3 to –5 mmol/L), moderate (–6 to –9 mmol/L), and severe (less than –10 mmol/L), and from this established a correlation between base deficit upon admission and transfusion requirements, the development of multiple organ failure, and death (Fig. 5-9).⁵⁶ Both base deficit and lactate correlate with the extent of shock and patient outcome, but interestingly do not firmly correlate with each other.^{57–59} Evaluation of both values may be useful in trauma patients with hemorrhage.

Although hematocrit changes may not rapidly reflect the total volume of blood loss, admission hematocrit has been shown to be associated with 24-hour fluid and transfusion requirements and more strongly associated with packed red blood cell transfusion than tachycardia, hypotension, or acidosis.⁶⁰ It must be noted that lack of a depression in the initial hematocrit does not rule out substantial blood loss or ongoing bleeding.

In management of trauma patients, understanding the patterns of injury of the patient in shock will help direct the evaluation and management. Identifying the sources of blood loss in patients with penetrating wounds is relatively simple because potential bleeding sources will be located along the known or suspected path of the wounding object. Patients with penetrating injuries who are in shock usually require operative intervention. Patients who suffer multisystem injuries from blunt trauma have multiple sources of potential hemorrhage. Blood loss sufficient to cause shock is generally of a large volume, and there are a limited number of sites that can harbor sufficient extravascular

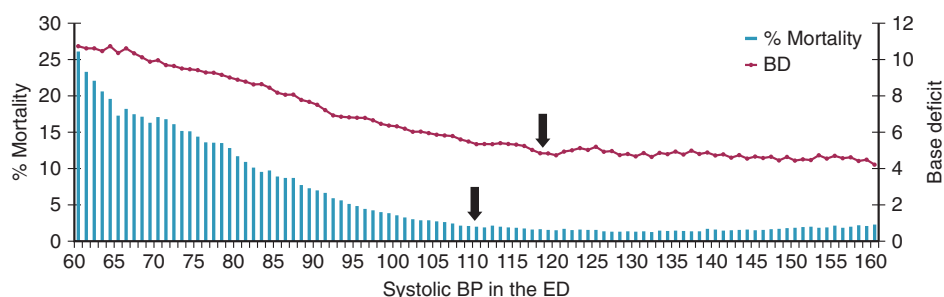


Figure 5-7. The relationship between systolic blood pressure and mortality in trauma patients with hemorrhage. These data suggest that a systolic blood pressure of less than 110 mmHg is a clinically relevant definition of hypotension and hypoperfusion based on an increasing rate of mortality below this pressure. Base deficit (BD) is also shown on this graph. ED = emergency department. (Reproduced with permission from Eastridge BJ, Salinas J, McManus JG, et al.⁵² Hypotension begins at 110 mmHg: redefining “hypotension” with data. *J Trauma*. 2007;63:291–297.)

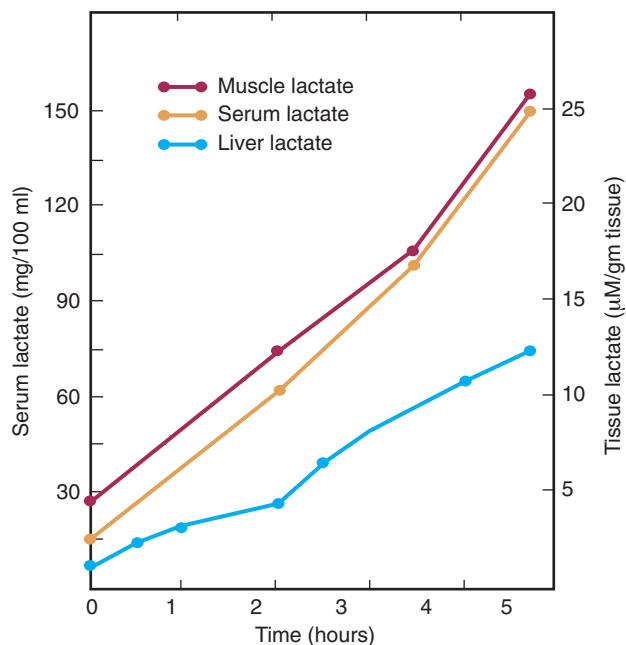


Figure 5-8. Progressive increases in serum lactate, muscle lactate, and liver lactate in a baboon model of hemorrhagic shock. (From Peitzman et al.,⁷ with permission. Reprinted with permission from the Journal of the American College of Surgeons, formerly Surgery Gynecology & Obstetrics)

blood volume to induce hypotension (e.g., external, intrathoracic, intra-abdominal, retroperitoneal, and long bone fractures). In the nontrauma patient, the GI tract must always be considered as a site for blood loss. Substantial blood loss externally may be suspected from prehospital medical reports documenting a substantial blood loss at the scene of an accident, history of massive blood loss from wounds, visible brisk bleeding, or presence of a large hematoma adjacent to an open wound. Injuries to major arteries or veins with associated open wounds may cause massive blood loss rapidly. Direct pressure must be applied and

sustained to minimize ongoing blood loss. Persistent bleeding from uncontrolled smaller vessels can, over time, precipitate shock if inadequately treated.

When major blood loss is not immediately visible in the setting of trauma, internal (intracavitary) blood loss should be suspected. Each pleural cavity can hold 2 to 3 L of blood and can therefore be a site of significant blood loss. Diagnostic and therapeutic tube thoracostomy may be indicated in unstable patients based on clinical findings and clinical suspicion. In a more stable patient, a chest radiograph may be obtained to look for evidence of hemothorax. Major retroperitoneal hemorrhage typically occurs in association with pelvic fractures, which is confirmed by pelvic radiography in the resuscitation bay. Intraperitoneal hemorrhage is probably the most common source of blood loss inducing shock. The physical exam for detection of substantial blood loss or injury is insensitive and unreliable; large volumes of intraperitoneal blood may be present before physical examination findings are apparent. Findings with intra-abdominal hemorrhage include abdominal distension, abdominal tenderness, or visible abdominal wounds. Hemodynamic abnormalities generally stimulate a search for blood loss before the appearance of obvious abdominal findings. Adjunctive tests are essential in the diagnosis of intraperitoneal bleeding; intraperitoneal blood may be rapidly identified by diagnostic ultrasound or diagnostic peritoneal lavage. Furthermore, patients who have sustained high-energy blunt trauma who are hemodynamically stable or who have normalized their vital signs in response to initial volume resuscitation should undergo computed tomography scans to assess for head, chest, and/or abdominal bleeding.

Treatment. Control of ongoing hemorrhage is an essential component of the resuscitation of the patient in shock. As mentioned in the earlier Diagnosis section, treatment of hemorrhagic shock is instituted concurrently with diagnostic evaluation to identify a source. Patients who fail to respond to initial resuscitative efforts should be assumed to have ongoing active hemorrhage from large vessels and require prompt

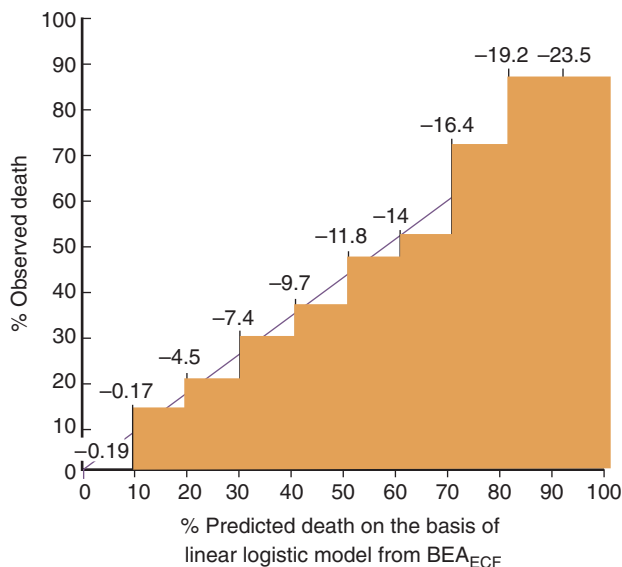
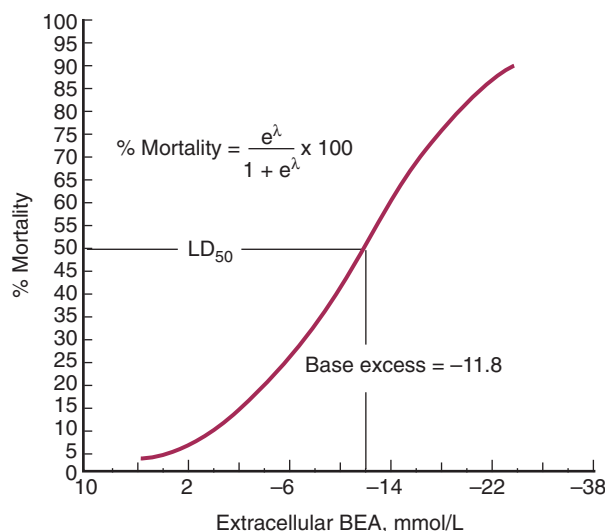


Figure 5-9. The relationship between base deficit (negative base excess) and mortality in trauma patients. BEA = base excess arterial; ECF = extracellular fluid. (Reproduced with permission from Siegel JH, Rivkind AI, Dalal S, et al. Early physiologic predictors of injury severity and death in blunt multiple trauma. Arch Surg. 1990;125:498. Copyright © 1990 American Medical Association. All rights reserved.)

operative intervention. Based on trauma literature, patients with ongoing hemorrhage demonstrate increased survival if the elapsed time between the injury and control of bleeding is decreased. Although there are no randomized controlled trials, retrospective studies provide compelling evidence in this regard. To this end, Clarke and colleagues⁶¹ demonstrated that trauma patients with major injuries isolated to the abdomen requiring emergency laparotomy had an increased probability of death with increasing length of time in the emergency department for patients who were in the emergency department for 90 minutes or less. This probability increased approximately 1% for each 3 minutes in the emergency department.

The appropriate priorities in these patients are (a) secure the airway, (b) control the source of blood loss, and (c) intravenous (IV) volume resuscitation. In trauma, identifying the body cavity harboring active hemorrhage will help focus operative efforts; however, because time is of the essence, rapid treatment is essential and diagnostic laparotomy or thoracotomy may be indicated. The actively bleeding patient cannot be resuscitated until control of ongoing hemorrhage is achieved. Our current understanding has led to the management strategy known as *damage control resuscitation*.⁶² This strategy begins in the emergency department and continues into the operating room and into the intensive care unit (ICU). Initial resuscitation is limited to keep SBP around 80 to 90 mmHg. This prevents renewed bleeding from recently clotted vessels. Resuscitation and intravascular volume resuscitation are accomplished with

4▶ blood products and limited crystalloids, which is addressed further later in this section. Too little volume allowing persistent severe hypotension and hypoperfusion is dangerous, yet too vigorous of a volume resuscitation may be just as deleterious. Control of hemorrhage is achieved in the operating room, and efforts to warm patients and to prevent coagulopathy using multiple blood products and pharmacologic agents are used in both the operating room and ICU.

Cannon and colleagues first made the observation that attempts to increase blood pressure in soldiers with uncontrolled sources of hemorrhage is counterproductive, with increased bleeding and higher mortality.³ This work was the foundation for the “hypotensive resuscitation” strategies. Several laboratory studies confirmed the observation that attempts to restore normal blood pressure with fluid infusion or vasopressors were rarely successful and resulted in more bleeding and higher mortality.⁶³ A prospective, randomized clinical study compared delayed fluid resuscitation (upon arrival in the operating room) with standard fluid resuscitation (with arrival by the paramedics) in hypotensive patients with penetrating torso injury.⁶⁴ The authors reported that delayed fluid resuscitation resulted in lower patient mortality. Further laboratory studies demonstrated that fluid restriction in the setting of profound hypotension resulted in early deaths from severe hypoperfusion. These studies also showed that aggressive crystalloid resuscitation attempting to normalize blood pressure resulted in marked hemodilution, with hematocrits of 5%.⁶³ Reasonable conclusions in the setting of uncontrolled hemorrhage include: Any delay in surgery for control of hemorrhage increases mortality; with uncontrolled hemorrhage attempting to achieve normal blood pressure may increase mortality, particularly with penetrating injuries and short transport times; a goal of SBP of 80 to 90 mmHg may be adequate in the patient with penetrating injury; and profound hemodilution should be avoided by early transfusion of red blood cells. For the patient with blunt injury, where the major

cause of death is a closed head injury, the increase in mortality with hypotension in the setting of brain injury must be avoided. In this setting, an SBP of 110 mmHg would seem to be more appropriate.

Patients who respond to initial resuscitative effort but then deteriorate hemodynamically frequently have injuries that require operative intervention. The magnitude and duration of their response will dictate whether diagnostic maneuvers can be performed to identify the site of bleeding. However, hemodynamic deterioration generally denotes ongoing bleeding for which some form of intervention (i.e., operation or interventional radiology) is required. Patients who have lost significant intravascular volume, but whose hemorrhage is controlled or has abated, often will respond to resuscitative efforts if the depth and duration of shock have been limited.

A subset of patients exists who fail to respond to resuscitative efforts despite adequate control of ongoing hemorrhage. These patients have ongoing fluid requirements despite adequate control of hemorrhage, have persistent hypotension despite restoration of intravascular volume necessitating vaso-
5▶ pressor support, and may exhibit a futile cycle of uncorrectable hypoperfusion, acidosis, and coagulopathy that cannot be interrupted despite maximum therapy. These patients have deteriorated to decompensated or irreversible shock with peripheral vasodilation and resistance to vasopressor infusion. Mortality is inevitable once the patient manifests shock in its terminal stages. Unfortunately, this is often diagnosed in retrospect.

Fluid resuscitation is a major adjunct to physically controlling hemorrhage in patients with shock. The ideal type of fluid to be used continues to be debated; however, crystalloids continue to be the mainstay of fluid choice. Several studies have demonstrated increased risk of death in bleeding trauma patients treated with colloid compared to patients treated with crystalloid.⁶⁵ In patients with severe hemorrhage, restoration of intravascular volume should be achieved with blood products.⁶⁶

Ongoing studies continue to evaluate the use of hypertonic saline as a resuscitative adjunct in bleeding patients.⁶⁷ The benefit of hypertonic saline solutions may be immunomodulatory. Specifically, these effects have been attributed to pharmacologic effects resulting in decreased reperfusion-mediated injury with decreased O₂ radical formation, less impairment of immune function compared to standard crystalloid solution, and less brain swelling in the multi-injured patient. The reduction of total volume used for resuscitation makes this approach appealing as a resuscitation agent for combat injuries and may contribute to a decrease in the incidence of ARDS and multiple organ failure.

Transfusion of packed red blood cells and other blood products is essential in the treatment of patients in hemorrhagic shock. Current recommendations in stable ICU patients aim for a target hemoglobin of 7 to 9 g/dL^{68,69}; however, no prospective randomized trials have compared restrictive and liberal transfusion regimens in trauma patients with hemorrhagic shock. The current standard in severely injured patients is termed damage control resuscitation and consists of transfusion with red blood cells, fresh frozen plasma (FFP), and platelet units given in equal number.⁷⁰ Civilian and military trauma data show that the development of coagulopathy of trauma is predictive of mortality.⁷¹ Data collected from a U.S. Army combat support hospital helped to propagate this practice, showing in patients who received massive transfusion of packed red blood cells (>10 units in 24 hours) that a high plasma-to-RBC ratio (1:1.4 units) was independently

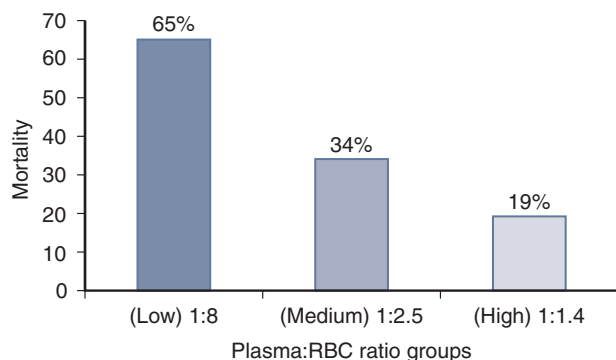


Figure 5-10. Increasing ratio of transfusion of fresh frozen plasma to red blood cells improves outcome of trauma patients receiving massive transfusions. RBC = red blood cell. (Reproduced with permission from Borgman MA, Spinella PC, Perkins JG, et al.⁷² *The ratio of blood products transfused affects mortality in patients receiving massive transfusions at a combat support hospital.* J Trauma. 2007;63:805-813.)

associated with improved survival (Fig. 5-10).⁷² A number of civilian studies have demonstrated similar results.⁷³ Similarly, platelet transfusion is important. Studies have demonstrated that low platelet counts in trauma patients were associated with increased mortality⁷⁴ and that increased platelet use appears to improve outcome.^{75,76} The benefit of platelet transfusion may be most pronounced in trauma patients with brain injury.⁷⁷ Platelets should be transfused in the bleeding patient to maintain counts above $50 \times 10^9/L$.

There is a potential role for other coagulation factor-based products, such as fibrinogen concentrates and prothrombin complex concentrates. Use of these agents may be guided by a drop in fibrinogen levels to less than 1 g/L or, less specifically, by thromboelastogram findings to suggest hyperfibrinolysis. Data also support the use of antifibrinolytic agents in bleeding trauma patients, specifically tranexamic acid (a synthetic lysine analogue that acts as a competitive inhibitor of plasmin and plasminogen). The multinational Clinical Randomization of an Antifibrinolytic in Significant Haemorrhage 2 (CRASH-2) trial suggested that early use of tranexamic acid limits rebleeding and reduces mortality⁷⁸ (Fig. 5-11). In the past, coagulopathy associated with the bleeding patient was presumed to be due solely to dilution and depletion of clotting factors and platelets. We now understand that an acute coagulopathy of trauma occurs as an immediate consequence of injury, with abnormal admission coagulation as a predictor of high mortality.⁷⁹ Traditional measurement of platelets, international normalized ratio, and partial thromboplastin time may not reflect the coagulopathy of trauma or response to therapy effectively. Recently, thromboelastography (TEG) has been used as a quicker, more comprehensive determination of coagulopathy and fibrinolysis in the injured patient. Holcomb and colleagues recently reported that TEG predicted patients with substantial bleeding and red cell transfusion better than conventional coagulopathy tests, need for platelet transfusion better than platelet count, and need for plasma transfusion better than fibrinogen levels.⁸⁰

Additional resuscitative adjuncts in patients with hemorrhagic shock include minimization of heat loss and maintaining normothermia. The development of hypothermia in the bleeding patient is associated with acidosis, hypotension, and coagulopathy.

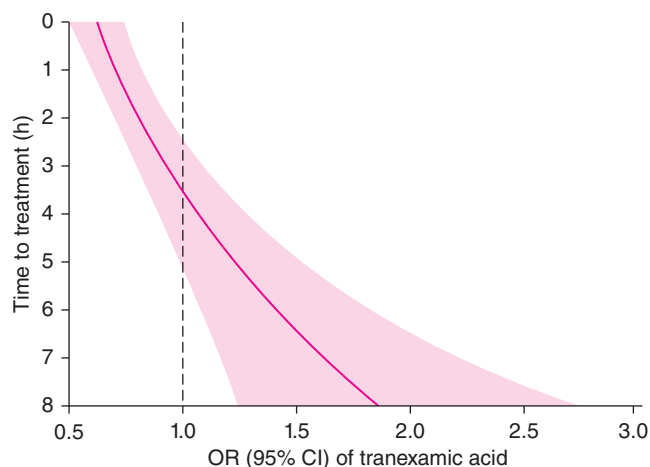


Figure 5-11. Early treatment (within 3 hours) of trauma patients with tranexamic acid reduces mortality. However, later treatment exacerbated outcome. OR = odds ratio. (Reprinted from Roberts I, Shakur H, Afolabi A, et al.⁷⁸ *The importance of early treatment with tranexamic acid in bleeding trauma patients: an exploratory analysis of the CRASH-2 randomised controlled trial.* The Lancet. 2011;377:1096-1101. Copyright ©2011 with permission from Elsevier.)

Hypothermia in bleeding trauma patients is an independent risk factor for bleeding and death. This likely is secondary to impaired platelet function and impairments in the coagulation cascade. Several studies have investigated the induction of controlled hypothermia in patients with severe shock based on the hypothesis of limiting metabolic activity and energy requirements, creating a state of “suspended animation.” These studies are promising and continue to be evaluated in large trials.

Traumatic Shock

The systemic response after trauma, combining the effects of soft tissue injury, long bone fractures, and blood loss, is clearly a different physiologic insult than simple hemorrhagic shock. Multiple organ failure, including ARDS, develops relatively often in the blunt trauma patient, but rarely after pure hemorrhagic shock (such as a GI bleed). The hypoperfusion deficit in traumatic shock is magnified by the proinflammatory activation that occurs following the induction of shock. In addition to ischemia or ischemia-reperfusion, accumulating evidence demonstrates that even simple hemorrhage induces proinflammatory activation that results in many of the cellular changes typically ascribed only to septic shock.^{81,82} At the cellular level, this may be attributable to the release of cellular products termed *damage-associated molecular patterns* (DAMPs; i.e., ribonucleic acid, uric acid, and high mobility group box 1) that activate the same set of cell surface receptors as bacterial products, initiating similar cell signaling.^{5,83} These receptors are termed *pattern recognition receptors* (PRRs) and include the TLR family of proteins. Examples of traumatic shock include small-volume hemorrhage accompanied by soft tissue injury (femur fracture, crush injury) or any combination of hypovolemic, neurogenic, cardiogenic, and obstructive shock that precipitates rapidly progressive proinflammatory activation. In laboratory models of traumatic shock, the addition of a soft tissue or long bone injury to hemorrhage produces lethality with significantly less blood loss when the animals are stressed by hemorrhage. Treatment of

traumatic shock is focused on correction of the individual elements to diminish the cascade of proinflammatory activation and includes prompt control of hemorrhage, adequate volume resuscitation to correct O₂ debt, débridement of nonviable tissue, stabilization of bony injuries, and appropriate treatment of soft tissue injuries.



Septic Shock (Vasodilatory Shock)

In the peripheral circulation, profound vasoconstriction is the typical physiologic response to the decreased arterial pressure and tissue perfusion with hemorrhage, hypovolemia, or acute heart failure. This is not the characteristic response in vasodilatory shock. Vasodilatory shock is the result of dysfunction of the endothelium and vasculature secondary to circulating inflammatory mediators and cells or as a response to prolonged and severe hypoperfusion. Thus, in vasodilatory shock, hypotension results from failure of the vascular smooth muscle to constrict appropriately. Vasodilatory shock is characterized by peripheral vasodilation with resultant hypotension and resistance to treatment with vasopressors. Despite the hypotension, plasma catecholamine levels are elevated, and the renin-angiotensin system is activated in vasodilatory shock. The most frequently encountered form of vasodilatory shock is septic shock. Other causes of vasodilatory shock include hypoxic lactic acidosis, carbon monoxide poisoning, decompensated and irreversible hemorrhagic shock, terminal cardiogenic shock, and postcardiotomy shock (Table 5-6). Thus, vasodilatory shock seems to represent the final common pathway for profound and prolonged shock of any etiology.⁸⁴

Despite advances in intensive care, the mortality rate for severe sepsis remains at 30% to 50%. In the United States, 750,000 cases of sepsis occur annually, one third of which are fatal.⁸⁵ Sepsis accounts for 9.3% of deaths in the United States, as many yearly as MI. Septic shock is a by-product of the body's response to disruption of the host-microbe equilibrium, resulting in invasive or severe localized infection.

In the attempt to eradicate the pathogens, the immune and other cell types (e.g., endothelial cells) elaborate soluble mediators that enhance macrophage and neutrophil killing effector mechanisms, increase procoagulant activity and fibroblast activity to localize the invaders, and increase microvascular blood flow to enhance delivery of killing forces to the area of invasion. When this response is overly exuberant or becomes systemic rather than localized, manifestations of sepsis may be evident.

Table 5-6

Causes of septic and vasodilatory shock

Systemic response to infection
Noninfectious systemic inflammation
Pancreatitis
Burns
Anaphylaxis
Acute adrenal insufficiency
Prolonged, severe hypotension
Hemorrhagic shock
Cardiogenic shock
Cardiopulmonary bypass
Metabolic
Hypoxic lactic acidosis
Carbon monoxide poisoning

These findings include enhanced cardiac output, peripheral vasodilation, fever, leukocytosis, hyperglycemia, and tachycardia. In septic shock, the vasodilatory effects are due, in part, to the upregulation of the inducible isoform of nitric oxide synthase (iNOS or NOS 2) in the vessel wall. iNOS produces large quantities of nitric oxide for sustained periods of time. This potent vasodilator suppresses vascular tone and renders the vasculature resistant to the effects of vasoconstricting agents.

Diagnosis. Attempts to standardize terminology have led to the establishment of criteria for the diagnosis of sepsis in the hospitalized adult. These criteria include manifestations of the host response to infection in addition to identification of an offending organism. The terms sepsis, severe sepsis, and septic shock are used to quantify the magnitude of the systemic inflammatory reaction. Patients with sepsis have evidence of an infection, as well as systemic signs of inflammation (e.g., fever, leukocytosis, and tachycardia). Hypoperfusion with signs of organ dysfunction is termed severe sepsis. Septic shock requires the presence of the above, associated with more significant evidence of tissue hypoperfusion and systemic hypotension. Beyond the hypotension, maldistribution of blood flow and shunting in the microcirculation further compromise delivery of nutrients to the tissue beds.^{86,87}

Recognizing septic shock begins with defining the patient at risk. The clinical manifestations of septic shock will usually become evident and prompt the initiation of treatment before bacteriologic confirmation of an organism or the source of an organism is identified. In addition to fever, tachycardia, and tachypnea, signs of hypoperfusion such as confusion, malaise, oliguria, or hypotension may be present. These should prompt an aggressive search for infection, including a thorough physical examination, inspection of all wounds, evaluation of intravascular catheters or other foreign bodies, obtaining appropriate cultures, and adjunctive imaging studies, as needed.

Treatment. Evaluation of the patient in septic shock begins with an assessment of the adequacy of their airway and ventilation. Severely obtunded patients and patients whose work of breathing is excessive require intubation and ventilation to prevent respiratory collapse. Because vasodilation and decrease in total peripheral resistance may produce hypotension, fluid resuscitation and restoration of circulatory volume with balanced salt solutions is essential. This resuscitation should be at least 30 mL/kg within the first 4 to 6 hours. Incremental fluid boluses should be continued based on the endpoint of resuscitation, including clearance of lactate. Starch-based colloid solutions should be avoided, as recent evidence suggests that these fluids may be deleterious in the setting of sepsis.^{86,88,89} Empiric antibiotics must be chosen carefully based on the most likely pathogens (gram-negative rods, gram-positive cocci, and anaerobes) because the portal of entry of the offending organism and its identity may not be evident until culture data return or imaging studies are completed. Knowledge of the bacteriologic profile of infections in an individual unit can be obtained from most hospital infection control departments and will suggest potential responsible organisms. Antibiotics should be tailored to cover the responsible organisms once culture data are available, and if appropriate, the spectrum of coverage narrowed. Long-term, empiric, broad-spectrum antibiotic use should be minimized to reduce the development of resistant organisms and to avoid the potential complications of fungal overgrowth and antibiotic-associated colitis from overgrowth of *Clostridium difficile*.

IV antibiotics will be insufficient to adequately treat the infectious episode in the settings of infected fluid collections, infected foreign bodies, and devitalized tissue. These situations require source control and involve percutaneous drainage and operative management to target a focus of infection. These situations may require multiple operations to ensure proper wound hygiene and healing.

After first-line therapy of the septic patient with antibiotics, IV fluids, and intubation if necessary, vasopressors may be necessary to treat patients with septic shock. Catecholamines are the vasopressors used most often, with norepinephrine being the first-line agent followed by epinephrine. Occasionally, patients with septic shock will develop arterial resistance to catecholamines. Arginine vasopressin, a potent vasoconstrictor, is often efficacious in this setting and is often added to norepinephrine.

The majority of septic patients have hyperdynamic physiology with supranormal cardiac output and low systemic vascular resistance. On occasion, septic patients may have low cardiac output despite volume resuscitation and even vasopressor support. Dobutamine therapy is recommended for patients with cardiac dysfunction as evidenced by high filling pressures and low cardiac output or clinical signs of hypoperfusion after achievement of restoration of blood pressure following fluid resuscitation. Mortality in this group is high. Despite the increasing incidence of septic shock over the past several decades, the overall mortality rates have changed little. Studies of interventions, including immunotherapy, resuscitation to pulmonary artery endpoints with hemodynamic optimization (cardiac output and O_2 delivery, even to supranormal values), and optimization of mixed venous O_2 measurements up to 72 hours after admission to the ICU, have not changed mortality.

Over the past decade, multiple advances have been made in the treatment of patients with sepsis and septic shock and collaborative groups such as the Surviving Sepsis Campaign continue to evaluate, modify, and put forth recommendations based on data (Fig. 5-12).⁸⁶ Negative results from previous studies have led to the suggestion that earlier interventions directed at improving global tissue oxygenation may be of benefit. To this end, Rivers and colleagues reported that goal-directed therapy of septic shock and severe sepsis initiated in the emergency department and continued for 6 hours significantly improved outcome.⁹⁰ This approach involved adjustment of cardiac preload, afterload, and contractility to balance O_2 delivery with O_2

demand. They found that goal-directed therapy during the first 6 hours of hospital stay (initiated in the emergency department) had significant effects, such as higher mean venous O_2 saturation, lower lactate levels, lower base deficit, higher pH, and decreased 28-day mortality (49.2% vs. 33.3%) compared to the standard therapy group. The frequency of sudden cardiovascular collapse was also significantly less in the group managed with goal-directed therapy (21.0% vs. 10.3%). Interestingly, the goal-directed therapy group received more IV fluids during the initial 6 hours, but the standard therapy group required more IV fluids by 72 hours. The authors emphasize that continued cellular and tissue decompensation is subclinical and often irreversible when obvious clinically. Goal-directed therapy allowed identification and treatment of these patients with insidious illness (global tissue hypoxia in the setting of normal vital signs).

Hyperglycemia and insulin resistance are typical in critically ill and septic patients, including patients without underlying diabetes mellitus. A recent study reported significant positive impact of tight glucose management on outcome in critically ill patients.⁹¹ The two treatment groups in this randomized, prospective study were assigned to receive intensive insulin therapy (maintenance of blood glucose between 80 and 110 mg/dL) or conventional treatment (infusion of insulin only if the blood glucose level exceeded 215 mg/dL, with a goal between 180 and 200 mg/dL). The mean morning glucose level was significantly higher in the conventional treatment as compared to the intensive insulin therapy group (153 vs. 103 mg/dL). Mortality in the intensive insulin treatment group (4.6%) was significantly lower than in the conventional treatment group (8.0%), representing a 42% reduction in mortality. This reduction in mortality was most notable in the patients requiring longer than 5 days in the ICU. Furthermore, intensive insulin therapy reduced episodes of septicemia by 46%, reduced duration of antibiotic therapy, and decreased the need for prolonged ventilatory support and renal replacement therapy.

Another treatment protocol that has been demonstrated to increase survival in patients with ARDS investigated the use of lower ventilatory tidal volumes compared to traditional tidal volumes.⁹² The majority of the patients enrolled in this multicenter, randomized trial developed ARDS secondary to pneumonia or sepsis. The trial compared traditional ventilation treatment, which involved an initial tidal volume of 12 mL/kg of predicted body weight, with ventilation with a lower tidal

Surviving Sepsis Campaign Bundles

To be Completed Within 3 Hours:

- 1) Measure lactate level
- 2) Obtain blood cultures prior to administration of antibiotics
- 3) Administer broad spectrum antibiotics
- 4) Administer 30 mL/kg crystalloid for hypotension or lactate ≥ 4 mmol/L

To be Completed Within 6 Hours:

- 5) Apply vasopressors (for hypotension that does not respond to initial fluid resuscitation) to maintain a mean arterial pressure (MAP) ≥ 65 mm Hg
- 6) In the event of persistent arterial hypotension despite volume resuscitation (septic shock) or initial lactate ≥ 4 mmol/L (36 mg/dL):
 - Measure central venous pressure (CVP)*
 - Measure central venous oxygen saturation (ScvO₂)*
- 7) Remeasure lactate if initial lactate was elevated*

*Targets for quantitative resuscitation included in the guidelines are CVP of ≥ 8 mm Hg, ScvO₂ of $\geq 70\%$, and normalization of lactate.

Figure 5-12. Updated bundles of care from the Surviving Sepsis Campaign 2012. (From Dellinger RP, Levy MM, Rhodes A, et al. Surviving Sepsis Campaign: international guidelines for management of severe sepsis and septic shock, 2012. Intensive Care Med. 2013;39:165-228, Figure 1. With kind permission from Springer Science + Business Media.)

volume, which involved an initial tidal volume of 6 mL/kg of predicted body weight. The trial was stopped after the enrollment of 861 patients because mortality was lower in the group treated with lower tidal volumes than in the group treated with traditional tidal volumes (31.0% vs. 39.8%, $P = .007$), and the number of days without ventilator use during the first 28 days after randomization was greater in this group (mean \pm SD, 12 ± 11 vs. 10 ± 11 days; $P = .007$). The investigators concluded that in patients with acute lung injury and ARDS, mechanical ventilation with a lower tidal volume than is traditionally used results in decreased mortality and increases the number of days without ventilator use. Additional strategies in ARDS management include higher levels of positive end expiratory pressure (PEEP), alveolar recruitment maneuvers, and prone positioning.

The use of corticosteroids in the treatment of sepsis and septic shock has been controversial for decades. The observation that severe sepsis often is associated with adrenal insufficiency or glucocorticoid receptor resistance has generated renewed interest in therapy for septic shock with corticosteroids. A single IV dose of 50 mg of hydrocortisone improved mean arterial blood pressure response relationships to norepinephrine and phenylephrine in patients with septic shock and was most notable in patients with relative adrenal insufficiency. A more recent study evaluated therapy with hydrocortisone (50 mg IV every 6 hours) and fludrocortisone (50 μ g orally once daily) versus placebo for 1 week in patients with septic shock.⁹³ As in earlier studies, the authors performed corticotropin tests on these patients to document and stratify patients by relative adrenal insufficiency. In this study, 7-day treatment with low doses of hydrocortisone and fludrocortisone significantly and safely lowered the risk of death in patients with septic shock and relative adrenal insufficiency. In an international, multicenter, randomized trial of corticosteroids in sepsis (CORTICUS study; 499 analyzable patients), steroids showed no benefit in intent-to-treat mortality or shock reversal.⁹⁴ This study suggested that hydrocortisone therapy cannot be recommended as routine adjuvant therapy for septic shock. However, if SBP remains less than 90 mmHg despite appropriate fluid and vasopressor therapy, hydrocortisone at 200 mg/d for 7 days in four divided doses or by continuous infusion should be considered.

Additional adjunctive immune modulation strategies have been developed for the treatment of septic shock. These include the use of antiendotoxin antibodies, anticytokine antibodies, cytokine receptor antagonists, immune enhancers, a non-isoform-specific nitric oxide synthase inhibitor, and O₂ radical scavengers. These compounds are each designed to alter some aspect of the host immune response to shock that is hypothesized to play a key role in its pathophysiology. However, most of these strategies have failed to demonstrate efficacy in human patients despite utility in well-controlled animal experiments. It is unclear whether the failure of these compounds is due to poorly designed clinical trials, inadequate understanding of the interactions of the complex host immune response to injury and infection, or animal models of shock that poorly represent the human disease.

Cardiogenic Shock

Cardiogenic shock is defined clinically as circulatory pump failure leading to diminished forward flow and subsequent tissue hypoxia, in the setting of adequate intravascular volume. Hemodynamic criteria include sustained hypotension (i.e., SBP <90 mmHg for at least 30 minutes), reduced cardiac index

(<2.2 L/min per square meter), and elevated pulmonary artery wedge pressure (>15 mmHg).⁹⁵ Mortality rates for cardiogenic shock are 50% to 80%. Acute, extensive MI is the most common cause of cardiogenic shock; a smaller infarction in a patient with existing left ventricular dysfunction also may precipitate shock. Cardiogenic shock complicates 5% to 10% of acute MIs. Conversely, cardiogenic shock is the most common cause of death in patients hospitalized with acute MI. Although shock may develop early after MI, it typically is not found on admission. Seventy-five percent of patients who have cardiogenic shock complicating acute MIs develop signs of cardiogenic shock within 24 hours after onset of infarction (average 7 hours).

Recognition of the patient with occult hypoperfusion is critical to prevent progression to obvious cardiogenic shock with its high mortality rate; early initiation of therapy to maintain blood pressure and cardiac output is vital. Rapid assessment, adequate resuscitation, and reversal of the myocardial ischemia are essential in optimizing outcome in patients with acute MI. Prevention of infarct extension is a critical component. Large segments of nonfunctional but viable myocardium contribute to the development of cardiogenic shock after MI. In the setting of acute MI, expeditious restoration of cardiac output is mandatory to minimize mortality; the extent of myocardial salvage possible decreases exponentially with increased time to restoration of coronary blood flow. The degree of coronary flow after percutaneous transluminal coronary angioplasty correlates with in-hospital mortality (i.e., 33% mortality with complete reperfusion, 50% mortality with incomplete reperfusion, and 85% mortality with absent reperfusion).⁹⁶ Inadequate cardiac function can be a direct result of cardiac injury, including profound myocardial contusion, blunt cardiac valvular injury, or direct myocardial damage (Table 5-7).⁹⁵⁻⁹⁸ The pathophysiology of cardiogenic shock involves a vicious cycle of myocardial ischemia that causes myocardial dysfunction, which results in more myocardial ischemia. When sufficient mass of the left ventricular wall is necrotic or ischemic and fails to pump, the stroke

Table 5-7

Causes of cardiogenic shock

Acute myocardial infarction
Pump failure
Mechanical complications
Acute mitral regurgitation
Acute ventricular septal defect
Free wall rupture
Pericardial tamponade
Arrhythmia
End-stage cardiomyopathy
Myocarditis
Severe myocardial contusion
Left ventricular outflow obstruction
Aortic stenosis
Hypertrophic obstructive cardiomyopathy
Obstruction to left ventricular filling
Mitral stenosis
Left atrial myxoma
Acute mitral regurgitation
Acute aortic insufficiency
Metabolic
Drug reactions

volume decreases. An autopsy series of patients dying from cardiogenic shock has found damage to 40% of the left ventricle.⁹⁹ Ischemia distant from the infarct zone may contribute to the systolic dysfunction in patients with cardiogenic shock. The majority of these patients have multivessel disease, with limited vasodilator reserve and pressure-dependent coronary flow in multiple areas of the heart. Myocardial diastolic function is impaired in cardiogenic shock as well. Decreased compliance results from myocardial ischemia, and compensatory increases in left ventricular filling pressures progressively occur.

Diminished cardiac output or contractility in the face of adequate intravascular volume (preload) may lead to underperfused vascular beds and reflexive sympathetic discharge. Increased sympathetic stimulation of the heart, either through direct neural input or from circulating catecholamines, increases heart rate, myocardial contraction, and myocardial O₂ consumption, which may not be relieved by increases in coronary artery blood flow in patients with fixed stenoses of the coronary arteries. Diminished cardiac output may also decrease coronary artery blood flow, resulting in a scenario of increased myocardial O₂ demand at a time when myocardial O₂ supply may be limited. Acute heart failure may also result in fluid accumulation in the pulmonary microcirculatory bed, decreasing myocardial O₂ delivery even further.

Diagnosis. Rapid identification of the patient with pump failure and institution of corrective action are essential in preventing the ongoing spiral of decreased cardiac output from injury causing increased myocardial O₂ needs that cannot be met, leading to progressive and unremitting cardiac dysfunction. In evaluation of possible cardiogenic shock, other causes of hypotension must be excluded, including hemorrhage, sepsis, pulmonary embolism, and aortic dissection. Signs of circulatory shock include hypotension, cool and mottled skin, depressed mental status, tachycardia, and diminished pulses. Cardiac exam may include dysrhythmia, precordial heave, or distal heart tones. Confirmation of a cardiac source for the shock requires electrocardiogram and urgent echocardiography. Other useful diagnostic tests include chest radiograph, arterial blood gases, electrolytes, complete blood count, and cardiac enzymes. Invasive cardiac monitoring, which generally is not necessary, can be useful to exclude right ventricular infarction, hypovolemia, and possible mechanical complications.

Making the diagnosis of cardiogenic shock involves the identification of cardiac dysfunction or acute heart failure in a susceptible patient. In the setting of blunt traumatic injury, hemorrhagic shock from intra-abdominal bleeding, intrathoracic bleeding, and bleeding from fractures must be excluded, before implicating cardiogenic shock from blunt cardiac injury. Relatively few patients with blunt cardiac injury will develop cardiac pump dysfunction. Those who do generally exhibit cardiogenic shock early in their evaluation. Therefore, establishing the diagnosis of blunt cardiac injury is secondary to excluding other etiologies for shock and establishing that cardiac dysfunction is present. Invasive hemodynamic monitoring with a pulmonary artery catheter may uncover evidence of diminished cardiac output and elevated pulmonary artery pressure.

Treatment. After ensuring that an adequate airway is present and ventilation is sufficient, attention should be focused on support of the circulation. Intubation and mechanical ventilation often are required, if only to decrease work of breathing and facilitate sedation of the patient. Rapidly excluding hypovolemia

and establishing the presence of cardiac dysfunction are essential. Treatment of cardiac dysfunction includes maintenance of adequate oxygenation to ensure adequate myocardial O₂ delivery and judicious fluid administration to avoid fluid overload and development of cardiogenic pulmonary edema. Electrolyte abnormalities, commonly hypokalemia and hypomagnesemia, should be corrected. Pain is treated with IV morphine sulfate or fentanyl. Significant dysrhythmias and heart block must be treated with antiarrhythmic drugs, pacing, or cardioversion, if necessary. Early consultation with cardiology is essential in current management of cardiogenic shock, particularly in the setting of acute MI.⁹⁵

When profound cardiac dysfunction exists, inotropic support may be indicated to improve cardiac contractility and cardiac output. Dobutamine primarily stimulates cardiac β_1 receptors to increase cardiac output but may also vasodilate peripheral vascular beds, lower total peripheral resistance, and lower systemic blood pressure through effects on β_2 receptors. Ensuring adequate preload and intravascular volume is therefore essential prior to instituting therapy with dobutamine. Dopamine stimulates receptors (vasoconstriction), β_1 receptors (cardiac stimulation), and β_2 receptors (vasodilation), with its effects on β receptors predominating at lower doses. Dopamine may be preferable to dobutamine in treatment of cardiac dysfunction in hypotensive patients. Tachycardia and increased peripheral resistance from dopamine infusion may worsen myocardial ischemia. Titration of both dopamine and dobutamine infusions may be required in some patients.

Epinephrine stimulates α and β receptors and may increase cardiac contractility and heart rate; however, it also may have intense peripheral vasoconstrictor effects that impair further cardiac performance. Catecholamine infusions must be carefully controlled to maximize coronary perfusion, while minimizing myocardial O₂ demand. Balancing the beneficial effects of impaired cardiac performance with the potential side effects of excessive reflex tachycardia and peripheral vasoconstriction requires serial assessment of tissue perfusion using indices such as capillary refill, character of peripheral pulses, adequacy of urine output, or improvement in laboratory parameters of resuscitation such as pH, base deficit, and lactate. Invasive monitoring generally is necessary in these unstable patients. The phosphodiesterase inhibitors amrinone and milrinone may be required on occasion in patients with resistant cardiogenic shock. These agents have long half-lives and induce thrombocytopenia and hypotension, and use is reserved for patients unresponsive to other treatment.

Patients whose cardiac dysfunction is refractory to cardiotonics may require mechanical circulatory support with an intra-aortic balloon pump.¹⁰⁰ Intra-aortic balloon pumping increases cardiac output and improves coronary blood flow by reduction of systolic afterload and augmentation of diastolic perfusion pressure. Unlike vasopressor agents, these beneficial effects occur without an increase in myocardial O₂ demand. An intra-aortic balloon pump can be inserted at the bedside in the ICU via the femoral artery through either a cutdown or using the percutaneous approach. Aggressive circulatory support of patients with cardiac dysfunction from intrinsic cardiac disease has led to more widespread application of these devices and more familiarity with their operation by both physicians and critical care nurses.

Preservation of existing myocardium and preservation of cardiac function are priorities of therapy for patients who have suffered an acute MI. Ensuring adequate oxygenation and O₂

delivery, maintaining adequate preload with judicious volume restoration, minimizing sympathetic discharge through adequate relief of pain, and correcting electrolyte imbalances are all straightforward nonspecific maneuvers that may improve existing cardiac function or prevent future cardiac complications. Anticoagulation and aspirin are given for acute MI. Although thrombolytic therapy reduces mortality in patients with acute MI, its role in cardiogenic shock is less clear. Patients in cardiac failure from an acute MI may benefit from pharmacologic or mechanical circulatory support in a manner similar to that of patients with cardiac failure related to blunt cardiac injury. Additional pharmacologic tools may include the use of β -blockers to control heart rate and myocardial O_2 consumption, nitrates to promote coronary blood flow through vasodilation, and ACE inhibitors to reduce ACE-mediated vasoconstrictive effects that increase myocardial workload and myocardial O_2 consumption.

Current guidelines of the American Heart Association recommend percutaneous transluminal coronary angiography for patients with cardiogenic shock, ST elevation, left bundle-branch block, and age less than 75 years.^{101,102} Early definition of coronary anatomy and revascularization is the pivotal step in treatment of patients with cardiogenic shock from acute MI.¹⁰³ When feasible, percutaneous transluminal coronary angioplasty (generally with stent placement) is the treatment of choice. Coronary artery bypass grafting seems to be more appropriate for patients with multiple vessel disease or left main coronary artery disease.

Obstructive Shock

Although obstructive shock can be caused by a number of different etiologies that result in mechanical obstruction of venous return (Table 5-8), in trauma patients, this is most commonly due to the presence of tension pneumothorax. Cardiac tamponade occurs when sufficient fluid has accumulated in the pericardial sac to obstruct blood flow to the ventricles. The hemodynamic abnormalities in pericardial tamponade are due to elevation of intracardiac pressures with limitation of ventricular filling in diastole with resultant decrease in cardiac output. Acutely, the pericardium does not distend; thus small volumes of blood may produce cardiac tamponade. If the effusion accumulates slowly (e.g., in the setting of uremia, heart failure, or malignant effusion), the quantity of fluid producing cardiac tamponade may reach 2000 mL. The major determinant of the degree of hypotension is the pericardial pressure. With either cardiac tamponade or tension pneumothorax, reduced filling

of the right side of the heart from either increased intrapleural pressure secondary to air accumulation (tension pneumothorax) or increased intrapericardial pressure precluding atrial filling secondary to blood accumulation (cardiac tamponade) results in decreased cardiac output associated with increased central venous pressure.

Diagnosis and Treatment. The diagnosis of tension pneumothorax should be made on clinical examination. The classic findings include respiratory distress (in an awake patient), hypotension, diminished breath sounds over one hemithorax, hyperresonance to percussion, jugular venous distention, and shift of mediastinal structures to the unaffected side with tracheal deviation. In most instances, empiric treatment with pleural decompression is indicated rather than delaying to wait for radiographic confirmation. When a chest tube cannot be immediately inserted, such as in the prehospital setting, the pleural space can be decompressed with a large-caliber needle. Immediate return of air should be encountered with rapid resolution of hypotension. Unfortunately, not all of the clinical manifestations of tension pneumothorax may be evident on physical examination. Hyperresonance may be difficult to appreciate in a noisy resuscitation area. Jugular venous distention may be absent in a hypovolemic patient. Tracheal deviation is a late finding and often is not apparent on clinical examination. Practically, three findings are sufficient to make the diagnosis of tension pneumothorax: respiratory distress or hypotension, decreased lung sounds, and hypertympany to percussion. Chest x-ray findings that may be visualized include deviation of mediastinal structures, depression of the hemidiaphragm, and hypo-opacification with absent lung markings. As discussed earlier, definitive treatment of a tension pneumothorax is immediate tube thoracostomy. The chest tube should be inserted rapidly, but carefully, and should be large enough to evacuate any blood that may be present in the pleural space. Most recommend placement in the fourth intercostal space (nipple level) at the anterior axillary line.

Cardiac tamponade results from the accumulation of blood within the pericardial sac, usually from penetrating trauma or chronic medical conditions such as heart failure or uremia. Although precordial wounds are most likely to injure the heart and produce tamponade, any projectile or wounding agent that passes in proximity to the mediastinum can potentially produce tamponade. Blunt cardiac rupture, a rare event in trauma victims who survive long enough to reach the hospital, can produce refractory shock and tamponade in the multiply-injured patient. The manifestations of cardiac tamponade, such as total circulatory collapse and cardiac arrest, may be catastrophic, or they may be more subtle. A high index of suspicion is warranted to make a rapid diagnosis. Patients who present with circulatory arrest from cardiac tamponade require emergency pericardial decompression, usually through a left thoracotomy. The indications for this maneuver are discussed in Chap. 7. Cardiac tamponade also may be associated with dyspnea, orthopnea, cough, peripheral edema, chest pain, tachycardia, muffled heart tones, jugular venous distention, and elevated central venous pressure. Beck's triad consists of hypotension, muffled heart tones, and neck vein distention. Unfortunately, absence of these clinical findings may not be sufficient to exclude cardiac injury and cardiac tamponade. Muffled heart tones may be difficult to appreciate in a busy trauma center, and jugular venous distention and central venous pressure may be diminished by coexistent bleeding. Therefore, patients at risk for cardiac tamponade

Table 5-8

Causes of obstructive shock

Pericardial tamponade
Pulmonary embolus
Tension pneumothorax
IVC obstruction
Deep venous thrombosis
Gravid uterus on IVC
Neoplasm
Increased intrathoracic pressure
Excess positive end-expiratory pressure
Neoplasm

IVC = inferior vena cava.

whose hemodynamic status permits additional diagnostic tests frequently require additional diagnostic maneuvers to confirm cardiac injury or tamponade.

Invasive hemodynamic monitoring may support the diagnosis of cardiac tamponade if elevated central venous pressure, pulsus paradoxus (i.e., decreased systemic arterial pressure with inspiration), or elevated right atrial and right ventricular pressure by pulmonary artery catheter is present. These hemodynamic profiles suffer from lack of specificity, the duration of time required to obtain them in critically injured patients, and their inability to exclude cardiac injury in the absence of tamponade. Chest radiographs may provide information on the possible trajectory of a projectile, but rarely are diagnostic because the acutely filled pericardium distends poorly. Echocardiography has become the preferred test for the diagnosis of cardiac tamponade. Good results in detecting pericardial fluid have been reported, but the yield in detecting pericardial fluid depends on the skill and experience of the ultrasonographer, body habitus of the patient, and absence of wounds that preclude visualization of the pericardium. Standard two-dimensional and transesophageal echocardiography are sensitive techniques to evaluate the pericardium for fluid and are typically performed by examiners skilled at evaluating ventricular function, valvular abnormalities, and integrity of the proximal thoracic aorta. Unfortunately, these skilled examiners are rarely immediately available at all hours of the night, when many trauma patients present; therefore, waiting for this test may result in inordinate delays. In addition, although both ultrasound techniques may demonstrate the presence of fluid or characteristic findings of tamponade (large volume of fluid, right atrial collapse, poor distensibility of the right ventricle), they do not exclude cardiac injury *per se*. Pericardiocentesis to diagnose pericardial blood and potentially relieve tamponade may be used. Performing pericardiocentesis under ultrasound guidance has made the procedure safer and more reliable. An indwelling catheter may be placed for several days in patients with chronic pericardial effusions. Needle pericardiocentesis may not evacuate clotted blood and has the potential to produce cardiac injury, making it a poor alternative in busy trauma centers.

Diagnostic pericardial window represents the most direct method to determine the presence of blood within the pericardium. The procedure is best performed in the operating room under general anesthesia. It can be performed through either the subxiphoid or transdiaphragmatic approach. Adequate equipment and personnel to rapidly decompress the pericardium, explore the injury, and repair the heart should be present. Once the pericardium is opened and tamponade relieved, hemodynamics usually improve dramatically and formal pericardial exploration can ensue. Exposure of the heart can be achieved by extending the incision to a median sternotomy, performing a left anterior thoracotomy, or performing bilateral anterior thoracotomies ("clamshell").

Neurogenic Shock

Neurogenic shock refers to diminished tissue perfusion as a result of loss of vasomotor tone to peripheral arterial beds. Loss of vasoconstrictor impulses results in increased vascular capacitance, decreased venous return, and decreased cardiac output. Neurogenic shock is usually secondary to spinal cord injuries from vertebral body fractures of the cervical or high thoracic region that disrupt sympathetic regulation of peripheral vascular tone (Table 5-9). Rarely, a spinal cord injury without

Table 5-9

Causes of neurogenic shock

Spinal cord trauma
Spinal cord neoplasm
Spinal/epidural anesthetic

bony fracture, such as an epidural hematoma impinging on the spinal cord, can produce neurogenic shock. Sympathetic input to the heart, which normally increases heart rate and cardiac contractility, and input to the adrenal medulla, which increases catecholamine release, may also be disrupted, preventing the typical reflex tachycardia that occurs with hypovolemia. Acute spinal cord injury results in activation of multiple secondary injury mechanisms: (a) vascular compromise to the spinal cord with loss of autoregulation, vasospasm, and thrombosis; (b) loss of cellular membrane integrity and impaired energy metabolism; and (c) neurotransmitter accumulation and release of free radicals. Importantly, hypotension contributes to the worsening of acute spinal cord injury as the result of further reduction in blood flow to the spinal cord. Management of acute spinal cord injury with attention to blood pressure control, oxygenation, and hemodynamics, essentially optimizing perfusion of an already ischemic spinal cord, seems to result in improved neurologic outcome. Patients with hypotension from spinal cord injury are best monitored in an ICU and carefully followed for evidence of cardiac or respiratory dysfunction.

Diagnosis. Acute spinal cord injury may result in bradycardia, hypotension, cardiac dysrhythmias, reduced cardiac output, and decreased peripheral vascular resistance. The severity of the spinal cord injury seems to correlate with the magnitude of cardiovascular dysfunction. Patients with complete motor injuries are over five times more likely to require vasopressors for neurogenic shock compared to those with incomplete lesions.¹⁰⁴ The classic description of neurogenic shock consists of decreased blood pressure associated with bradycardia (absence of reflexive tachycardia due to disrupted sympathetic discharge), warm extremities (loss of peripheral vasoconstriction), motor and sensory deficits indicative of a spinal cord injury, and radiographic evidence of a vertebral column fracture. Patients with multisystem trauma that includes spinal cord injuries often have head injuries that may make identification of motor and sensory deficits difficult in the initial evaluation. Furthermore, associated injuries may occur that result in hypovolemia, further complicating the clinical presentation. In a subset of patients with spinal cord injuries from penetrating wounds, most of the patients with hypotension had blood loss as the etiology (74%) rather than neurogenic causes, and few (7%) had the classic findings of neurogenic shock.¹⁰⁵ In the multiply injured patient, other causes of hypotension, including hemorrhage, tension pneumothorax, and cardiogenic shock, must be sought and excluded.

Treatment. After the airway is secured and ventilation is adequate, fluid resuscitation and restoration of intravascular volume often will improve perfusion in neurogenic shock. Most patients with neurogenic shock will respond to restoration of intravascular volume alone, with satisfactory improvement in perfusion and resolution of hypotension. Administration of vasoconstrictors will improve peripheral vascular tone, decrease vascular capacitance, and increase venous return, but should only be considered once hypovolemia is excluded as the cause of the

hypotension and the diagnosis of neurogenic shock established. If the patient's blood pressure has not responded to what is felt to be adequate volume resuscitation, dopamine may be used first. A pure α agonist, such as phenylephrine, may be used primarily or in patients unresponsive to dopamine. Specific treatment for the hypotension is often of brief duration, as the need to administer vasoconstrictors typically lasts 24 to 48 hours. On the other hand, life-threatening cardiac dysrhythmias and hypotension may occur up to 14 days after spinal cord injury.

The duration of the need for vasopressor support for neurogenic shock may correlate with the overall prognosis or chances of improvement in neurologic function. Appropriate rapid restoration of blood pressure and circulatory perfusion may improve perfusion to the spinal cord, prevent progressive spinal cord ischemia, and minimize secondary cord injury. Restoration of normal blood pressure and adequate tissue perfusion should precede any operative attempts to stabilize the vertebral fracture.

ENDPOINTS IN RESUSCITATION

Shock is defined as inadequate perfusion to maintain normal organ function. With prolonged anaerobic metabolism, tissue acidosis and O_2 debt accumulate. Thus, the goal in the treatment of shock is restoration of adequate organ perfusion and tissue oxygenation. Resuscitation is complete when O_2 debt is repaid, tissue acidosis is corrected, and aerobic metabolism is restored. Clinical confirmation of this endpoint remains a challenge.

Resuscitation of the patient in shock requires simultaneous evaluation and treatment; the etiology of the shock often is not initially apparent. Hemorrhagic shock, septic shock, and traumatic shock are the most common types of shock encountered on surgical services. To optimize outcome in bleeding patients, early control of the hemorrhage and adequate volume resuscitation, including both red blood cells and crystalloid solutions, are necessary. Expedient operative resuscitation is mandatory to limit the magnitude of activation of multiple mediator systems and to abort the microcirculatory changes, which may evolve insidiously into the cascade that ends in irreversible hemorrhagic shock. Attempts to stabilize an actively bleeding patient anywhere but in the operating room are inappropriate. Any intervention that delays the patient's arrival in the operating room for control of hemorrhage increases mortality, thus the important concept of *operating room resuscitation* of the critically injured patient.

Recognition by care providers of the patient who is in the compensated phase of shock is equally important, but more difficult based on clinical criteria. Compensated shock exists when inadequate tissue perfusion persists despite normalization of blood pressure and heart rate. Even with normalization of blood pressure, heart rate, and urine output, 80% to 85% of trauma patients have inadequate tissue perfusion, as evidenced by increased lactate or decreased mixed venous O_2 saturation.^{55,106} Persistent, occult hypoperfusion is frequent in the ICU, with a resultant significant increase in infection rate and mortality in major trauma patients. Patients failing to reverse their lactic acidosis within 12 hours of admission (acidosis that was persistent despite normal heart rate, blood pressure, and urine output) developed an infection three times as often as those who normalized their lactate levels within 12 hours of admission. In addition, mortality was fourfold higher in patients who developed infections. Both injury severity score and occult hypotension

Table 5-10

Endpoints in resuscitation

Systemic/global
Lactate
Base deficit
Cardiac output
Oxygen delivery and consumption
Tissue specific
Gastric tonometry
Tissue pH, oxygen, carbon dioxide levels
Near infrared spectroscopy
Cellular
Membrane potential
Adenosine triphosphate

(lactic acidosis) longer than 12 hours were independent predictors of infection.¹⁰⁷ Thus, recognition of subclinical hypoperfusion requires information beyond vital signs and urinary output.

Endpoints in resuscitation can be divided into *systemic* or *global parameters*, *tissue-specific parameters*, and *cellular parameters*. Global endpoints include vital signs, cardiac output, pulmonary artery wedge pressure, O_2 delivery and consumption, lactate, and base deficit (Table 5-10).

Assessment of Endpoints in Resuscitation

Inability to repay O_2 debt is a predictor of mortality and organ failure; the probability of death has been directly correlated to the calculated O_2 debt in hemorrhagic shock. Direct measurement of the O_2 debt in the resuscitation of patients is difficult. The easily obtainable parameters of arterial blood pressure, heart rate, urine output, central venous pressure, and pulmonary artery occlusion pressure are poor indicators of the adequacy of tissue perfusion. Therefore, surrogate parameters have been sought to estimate the O_2 debt; serum lactate and base deficit have been shown to correlate with O_2 debt.

Lactate. Lactate is generated by conversion of pyruvate to lactate by lactate dehydrogenase in the setting of insufficient O_2 . Lactate is released into the circulation and is predominantly taken up and metabolized by the liver and kidneys. The liver accounts for approximately 50% and the kidney for about 30% of whole body lactate uptake. Elevated serum lactate is an indirect measure of the O_2 debt, and therefore an approximation of the magnitude and duration of the severity of shock. The admission lactate level, highest lactate level, and time interval to normalize the serum lactate are important prognostic indicators for survival. For example, in a study of 76 consecutive patients, 100% survival was observed among the patients with normalization of lactate within 24 hours, 78% survival when lactate normalized between 24 and 48 hours, and only 14% survivorship if it took longer than 48 hours to normalize the serum lactate.⁵⁵ In contrast, individual variability of lactate may be too great to permit accurate prediction of outcome in any individual case. Base deficit and volume of blood transfusion required in the first 24 hours of resuscitation may be better predictors of mortality than the plasma lactate alone.

Base Deficit. Base deficit is the amount of base in millimoles that is required to titrate 1 L of whole blood to a pH of 7.40 with the sample fully saturated with O_2 at 37°C (98.6°F) and

a partial pressure of CO₂ of 40 mmHg. It usually is measured by arterial blood gas analysis in clinical practice as it is readily and quickly available. The mortality of trauma patients can be stratified according to the magnitude of base deficit measured in the first 24 hours after admission.⁶⁰ In a retrospective study of over 3000 trauma admissions, patients with a base deficit worse than 15 mmol/L had a mortality of 70%. Base deficit can be stratified into mild (3–5 mmol/L), moderate (6–14 mmol/L), and severe (15 mmol/L) categories, with a trend toward higher mortality with worsening base deficit in patients with trauma. Both the magnitude of the perfusion deficit as indicated by the base deficit and the time required to correct it are major factors determining outcome in shock.

Indeed, when elevated base deficit persists (or lactic acidosis) in the trauma patient, ongoing bleeding is often the etiology. Trauma patients admitted with a base deficit greater than 15 mmol/L required twice the volume of fluid infusion and six times more blood transfusion in the first 24 hours compared to patients with mild acidosis. Transfusion requirements increased as base deficit worsened, and ICU and hospital lengths of stay increased. Mortality increased as base deficit worsened; the frequency of organ failure increased with greater base deficit.⁵⁶ The probability of trauma patients developing ARDS has been reported to correlate with severity of admission base deficit and lowest base deficit within the first 24 hours postinjury.⁵⁸ Persistently high base deficit is associated with abnormal O₂ utilization and higher mortality. Monitoring base deficit in the resuscitation of trauma patients assists in assessment of O₂ transport and efficacy of resuscitation.⁵⁷

Factors that may compromise the utility of the base deficit in estimating O₂ debt are the administration of bicarbonate, hypothermia, hypocapnia (overventilation), heparin, ethanol, and ketoacidosis. However, the base deficit remains one of the most widely used estimates of O₂ debt for its clinical relevance, accuracy, and availability.

Gastric Tonometry. Lactate and base deficit indicate global tissue acidosis. Several authors have suggested that tissue-specific endpoints, rather than systemic endpoints, are more predictive of outcome and adequate resuscitation in trauma patients. With heterogeneity of blood flow, regional tissue beds may be hypoperfused. Gastric tonometry has been used to assess perfusion of the GI tract. The concentration of CO₂ accumulating in the gastric mucosa can be sampled with a specially designed nasogastric tube. With the assumption that gastric bicarbonate is equal to serum levels, gastric intramucosal pH (pHi) is calculated by applying the Henderson-Hasselbalch equation. pHi should be greater than 7.3; pHi will be lower in the setting of decreased O₂ delivery to the tissues. pHi is a good prognostic indicator; patients with normal pHi have better outcomes than those patients with pHi less than 7.3.^{108,109} Goal-directed human studies, with pHi as an endpoint in resuscitation, have shown normalization of pHi to correlate with improved outcome in several studies and with contradictory findings in other studies. Use of pHi as a singular endpoint in the resuscitation of critically ill patients remains controversial.¹¹⁰

Near Infrared Spectroscopy. Near infrared (NIR) spectroscopy can measure tissue oxygenation and redox state of cytochrome a,a₃ on a continuous, noninvasive basis. The NIR probe emits multiple wavelengths of light in the NIR spectrum (650 to 1100 nm). Photons are then either absorbed by the tissue or reflected back to the probe. Maximal exercise in laboratory studies

resulted in reduction of cytochrome a,a₃; this correlated with tissue lactate elevation. NIR spectroscopy can be used to compare tissue oxyhemoglobin levels (indicating tissue O₂ supply to cytochrome a,a₃ with mitochondrial O₂ consumption), thus demonstrating flow-independent mitochondrial oxidative dysfunction and the need for further resuscitation. Trauma patients with decoupled oxyhemoglobin and cytochrome a,a₃ have redox dysfunction and have been shown to have a higher incidence of organ failure (89% vs. 13%).^{111,112}

Tissue PH, Oxygen, and Carbon Dioxide Concentration. Tissue probes with optical sensors have been used to measure tissue pH and partial pressure of O₂ and CO₂ in subcutaneous sites, muscle, and the bladder. These probes may use transcutaneous methodology with Clark electrodes or direct percutaneous probes.^{113,114} The percutaneous probes can be inserted through an 18-gauge catheter and hold promise as continuous monitors of tissue perfusion.

Right Ventricular End-Diastolic Volume Index. Right ventricular end-diastolic volume index (RVEDVI) seems to more accurately predict preload for cardiac index than does pulmonary artery wedge pressure.¹¹⁵ Chang and colleagues reported that 50% of trauma patients had persistent splanchnic ischemia that was reversed by increasing RVEDVI. RVEDVI is a parameter that seems to correlate with preload-related increases in cardiac output. More recently, these authors have described left ventricular power output as an endpoint (LVP >320 mmHg·L/min per square meter), which is associated with improved clearance of base deficit and a lower rate of organ dysfunction following injury.¹¹⁶

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chapter

Surgical Infections

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HISTORICAL BACKGROUND

Although treatment of infection has been an integral part of the surgeon's practice since the dawn of time, the body of knowledge that led to the present field of surgical infectious disease was derived from the evolution of germ theory and antisepsis. Application of the latter to clinical practice, concurrent with the development of anesthesia, was pivotal in allowing surgeons to expand their repertoire to encompass complex procedures that previously were associated with extremely high rates of morbidity and mortality due to postoperative infections. However, until recently the occurrence of infection related to the surgical wound was the rule rather than the exception. In fact, the development of modalities to effectively prevent and treat infection has occurred only within the last several decades.

A number of observations by nineteenth-century physicians and investigators were critical to our current understanding of the pathogenesis, prevention, and treatment of surgical infections. In 1846, Ignaz Semmelweis, a Magyar physician, took a post at the Allgemeines Krankenhaus in Vienna. He noticed that the mortality from puerperal ("childbed") fever was much higher in the teaching ward (1:11) than in the ward where patients were delivered by midwives (1:29). He also made the interesting observation that women who delivered prior to arrival on the teaching ward had a negligible mortality rate. The tragic death of a colleague due to overwhelming infection after a knife scratch received during an autopsy of a woman who had died of puerperal fever led Semmelweis to observe that pathologic changes in his friend were identical to those of women dying from this postpartum disease. He then hypothesized that puerperal fever was caused by putrid material transmitted from patients dying of this disease by carriage on the examining fingers of the medical students and physicians who frequently went from the autopsy room to the wards. The low mortality noted in the midwives' ward, Semmelweis realized, was

because midwives did not participate in autopsies. Fired with the zeal of his revelation, he posted a notice on the door to the ward requiring all caregivers to rinse their hands thoroughly in chlorine water prior to entering the area. This simple intervention reduced mortality from puerperal fever to 1.5%, surpassing the record of the midwives. In 1861, he published his classic work on childbed fever based on records from his practice. Unfortunately, Semmelweis' ideas were not well accepted by the authorities of the time.¹ Increasingly frustrated by the indifference of the medical profession, he began writing open letters to well-known obstetricians in Europe, and was committed to an asylum due to concerns that he was losing his mind. He died shortly thereafter. His achievements were only recognized after Pasteur's description of the germ theory of disease.

Louis Pasteur performed a body of work during the latter part of the nineteenth century that provided the underpinnings of modern microbiology, at the time known as "germ theory." His work in humans followed experiments identifying infectious agents in silkworms. He was able to elucidate the principle that contagious diseases are caused by specific microbes and that these microbes are foreign to the infected organism. Using this principle he developed techniques of sterilization critical to oenology, and identified several bacteria responsible for human illnesses, including *Staphylococcus* and *Streptococcus pneumoniae* (pneumococcus).

Joseph Lister, the son of a wine merchant, was appointed professor of surgery at the Glasgow Royal Infirmary in 1859. In his early practice, he noted that over 50% of his patients undergoing amputation died because of postoperative infection. After hearing of Pasteur's theory, Lister experimented with the use of a solution of carbolic acid, which he knew was being used to treat sewage. He first reported his findings to the British Medical Association in 1867 using dressings saturated with carbolic acid on 12 patients with compound fractures; 10 recovered

Key Points

- 1► Sepsis is both the presence of infection and the host response to infection (systemic inflammatory response syndrome, SIRS). Sepsis is a clinical spectrum, ranging from sepsis (SIRS plus infection) to severe sepsis (organ dysfunction), to septic shock (hypotension requiring vasopressors). Outcomes in patients with sepsis are improved with an organized approach to therapy that includes rapid resuscitation, antibiotics, and source control.
- 2► Source control is a key concept in the treatment of most surgically relevant infections. Infected or necrotic material must be drained or removed as part of the treatment plan in this setting. Delays in adequate source control are associated with worsened outcomes.
- 3► Principles relevant to appropriate antibiotic prophylaxis for surgery: (a) select an agent with activity against organisms commonly found at the site of surgery, (b) the initial dose of the antibiotic should be given within 30 minutes prior to the creation of the incision, (c) the antibiotic should be redosed during long operations based upon the half-life of the agent to ensure adequate tissue levels, and (d) the antibiotic regimen should not be continued for more than 24 hours after surgery for routine prophylaxis.
- 4► When using antimicrobial agents for therapy of serious infection, several principles should be followed: (a) identify likely sources of infection, (b) select an agent (or agents) that will have efficacy against likely organisms for these sources, (c) inadequate or delayed antibiotic therapy results in increased mortality, so it is important to begin therapy rapidly with broader coverage, (d) when possible, obtain cultures early and use results to refine therapy, (e) if no infection is identified after 3 days, strongly consider discontinuation of antibiotics, based upon the patient's clinical course, (f) discontinue antibiotics after an appropriate course of therapy.
- 5► The incidence of surgical site infections can be reduced by appropriate patient preparation, timely perioperative antibiotic administration, maintenance of perioperative normothermia and normoglycemia, and appropriate wound management.
- 6► The keys to good outcomes in patients with necrotizing soft tissue infection are early recognition and appropriate debridement of infected tissue with repeated debridement until no further signs of infection are present.
- 7► Transmission of HIV and other infections spread by blood and body fluid from patient to health care worker can be minimized by observation of universal precautions, which include routine use of barriers when anticipating contact with blood or body fluids, washing of hands and other skin surfaces immediately after contact with blood or body fluids, and careful handling and disposal of sharp instruments during and after use.

without amputation, one survived with amputation, and one died of causes unrelated to the wound. In spite of initial resistance, his methods were quickly adopted throughout Europe.

From 1878 until 1880, Robert Koch was the District Medical Officer for Wollstein, which was an area in which anthrax was endemic. Performing experiments in his home, without the benefit of scientific equipment and academic contact, Koch developed techniques for culture of *Bacillus anthracis* and proved the ability of this organism to cause anthrax in healthy animals. He developed the following four postulates to identify the association of organisms with specific diseases: (a) the suspected pathogenic organism should be present in all cases of the disease and absent from healthy animals, (b) the suspected pathogen should be isolated from a diseased host and grown in a pure culture in vitro, (c) cells from a pure culture of the suspected organism should cause disease in a healthy animal, and (d) the organism should be reisolated from the newly diseased animal and shown to be the same as the original. He used these same techniques to identify the organisms responsible for cholera and tuberculosis. During the next century, Koch's postulates, as they came to be called, became critical to our understanding of surgical infections and remain so today.²

The first intra-abdominal operation to treat infection via "source control" (i.e., surgical intervention to eliminate the source of infection) was appendectomy. This operation was pioneered by Charles McBurney at the New York College of Physicians and Surgeons, among others.³ McBurney's classic report on early operative intervention for appendicitis was presented before the New York Surgical Society in 1889. Appendectomy for the treatment of appendicitis, previously an often fatal disease, was popularized after the 1902 coronation of King

Edward VII of England was delayed due to his need for an appendectomy, which was performed by Sir Frederick Treves. The king desperately needed an appendectomy but strongly opposed going into the hospital, protesting, "I have a coronation on hand." However, Treves was adamant, stating, "It will be a funeral, if you don't have the operation." Treves carried the debate, and the king lived.

During the twentieth century the discovery of effective antimicrobials added another tool to the armamentarium of modern surgeons. Sir Alexander Fleming, after serving in the British Army Medical Corps during World War I, continued work on the natural antibacterial action of the blood and antiseptics. In 1928, while studying influenza virus, he noted a zone of inhibition around a mold colony (*Penicillium notatum*) that serendipitously grew on a plate of *Staphylococcus*, and he named the active substance penicillin. This first effective antibacterial agent subsequently led to the development of hundreds of potent antimicrobials, set the stage for their use as prophylaxis against postoperative infection, and became a critical component of the armamentarium to treat aggressive, lethal surgical infections.

Concurrent with the development of numerous antimicrobial agents were advances in the field of clinical microbiology. Many new microbes were identified, including numerous anaerobes; the autochthonous microflora of the skin, gastrointestinal tract, and other parts of the body that the surgeon encountered in the process of an operation were characterized in great detail. However, it remained unclear whether these organisms, anaerobes in particular, were commensals or pathogens. Subsequently, the initial clinical observations of surgeons such as Frank Meleney, William Altemeier, and others provided the key, when they observed that aerobes and anaerobes could

synergize to cause serious soft tissue and severe intra-abdominal infection.^{4,5} Thus, the concepts that resident microbes were nonpathogenic until they entered a sterile body cavity at the time of surgery, and that many, if not most, surgical infections were polymicrobial in nature, became critical ideas, and were promulgated by a number of clinician-scientists over the last several decades.^{6,7} These tenets became firmly established after microbiology laboratories demonstrated the invariable presence of aerobes and anaerobes in peritoneal cultures obtained at the time of surgery for intra-abdominal infection due to a perforated viscus or gangrenous appendicitis. Clinical trials provided ample evidence that optimal therapy for these infections required effective source control, plus the administration of antimicrobial agents directed against both types of pathogens.

William Osler, a prolific writer and one of the fathers of American medicine, made an observation in 1904 in his treatise *The Evolution of Modern Medicine* that was to have profound implications for the future of treatment of infection: “Except on few occasions, the patient appears to die from the body’s response to infection rather than from it.”⁸ The discovery of the first cytokines began to allow insight into the human organism’s response to infection, and led to an explosion in our understanding of the host inflammatory response. Expanding knowledge of the multiple pathways activated during the response to invasion by infectious organisms has permitted the design of new therapies targeted at modifying the inflammatory response to infection, which seems to cause much of the organ dysfunction and failure. Preventing and treating this process of multiple organ failure during infection is one of the major challenges of modern critical care and surgical infectious disease.

PATHOGENESIS OF INFECTION

Host Defenses

The mammalian host possesses several layers of endogenous defense mechanisms that serve to prevent microbial invasion, limit proliferation of microbes within the host, and contain or eradicate invading microbes. These defenses are integrated and redundant so that the various components function as a complex, highly regulated system that is extremely effective in coping with microbial invaders. They include site-specific defenses that function at the tissue level, as well as components that freely circulate throughout the body in both blood and lymph. Systemic host defenses invariably are recruited to a site of infection, a process that begins immediately upon introduction of microbes into a sterile area of the body. Perturbation of one or more components of these defenses (e.g., via immunosuppressants, foreign body, chronic illness, and burns) may have substantial negative impact on resistance to infection.

Entry of microbes into the mammalian host is precluded by the presence of a number of barriers that possess either an epithelial (integument) or mucosal (respiratory, gut, and urogenital) surface. Barrier function, however, is not solely limited to physical characteristics. Host barrier cells may secrete substances that limit microbial proliferation or prevent invasion. Also, resident or commensal microbes (endogenous or autochthonous host microflora) adherent to the physical surface and to each other may preclude invasion, particularly of virulent organisms (colonization resistance).⁹

The most extensive physical barrier is the integument or skin. In addition to the physical barrier posed by the epithelial

surface, the skin harbors its own resident microflora that may block the attachment and invasion of noncommensal microbes. Microbes are also held in check by chemicals that sebaceous glands secrete and by the constant shedding of epithelial cells. The endogenous microflora of the integument primarily comprises gram-positive aerobic microbes belonging to the genera *Staphylococcus* and *Streptococcus*, as well as *Corynebacterium* and *Propionibacterium* species. These organisms plus *Enterococcus faecalis* and *faecium*, *Escherichia coli* and other Enterobacteriaceae, and yeast such as *Candida albicans* can be isolated from the infraumbilical regions of the body. Diseases of the skin (e.g., eczema and dermatitis) are associated with overgrowth of skin commensal organisms, and barrier breaches invariably lead to the introduction of these microbes.

The respiratory tract possesses several host defense mechanisms that facilitate the maintenance of sterility in the distal bronchi and alveoli under normal circumstances. In the upper respiratory tract, respiratory mucus traps larger particles, including microbes. This mucus is then passed into the upper airways and oropharynx by ciliated epithelial cells, where the mucus is cleared via coughing. Smaller particles arriving in the lower respiratory tract are cleared via phagocytosis by pulmonary alveolar macrophages. Any process that diminishes these host defenses can lead to development of bronchitis or pneumonia.

The urogenital, biliary, pancreatic ductal, and distal respiratory tracts do not possess resident microflora in healthy individuals, although microbes may be present if these barriers are affected by disease (e.g., malignancy, inflammation, calculi, or foreign body), or if microorganisms are introduced from an external source (e.g., urinary catheter or pulmonary aspiration). In contrast, significant numbers of microbes are encountered in many portions of the gastrointestinal tract, with vast numbers being found within the oropharynx and distal colon or rectum, although the specific organisms differ.

One would suppose that the entire gastrointestinal tract would be populated via those microbes found in the oropharynx, but this is not the case.⁹ This is because after ingestion these organisms routinely are killed in the highly acidic, low-motility environment of the stomach during the initial phases of digestion. Thus, small numbers of microbes populate the gastric mucosa $\sim 10^2$ to 10^3 colony-forming units (CFU)/mL. This population expands in the presence of drugs or disease states that diminish gastric acidity. Microbes that are not destroyed within the stomach enter the small intestine, in which a certain amount of microbial proliferation takes place, such that approximately 10^5 to 10^8 CFU/mL are present in the terminal ileum.

The relatively low-oxygen, static environment of the colon is accompanied by the exponential growth of microbes that comprise the most extensive host endogenous microflora. Anaerobic microbes outnumber aerobic species approximately 100:1 in the distal colon, and approximately 10^{11} to 10^{12} CFU/g are present in feces. Large numbers of facultative and strict anaerobes (*Bacteroides fragilis*, *distasonis*, and *thetaiotaomicron*, *Bifidobacterium*, *Clostridium*, *Eubacterium*, *Fusobacterium*, *Lactobacillus*, and *Peptostreptococcus* species) as well as several orders of magnitude fewer aerobic microbes (*Escherichia coli* and other Enterobacteriaceae, *Enterococcus faecalis* and *faecium*, *Candida albicans* and other *Candida* spp.) are present. Intriguingly, although colonization resistance on the part of this extensive, well-characterized host microflora effectively prevents invasion of enteric pathogens such as *Salmonella*, *Shigella*, *Vibrio*, and other enteropathogenic bacterial species, these same organisms

provide the initial inoculum for infection should perforation of the gastrointestinal tract occur. It is of great interest that only some of these microbial species predominate in established intra-abdominal infections.

Once microbes enter a sterile body compartment (e.g., pleural or peritoneal cavity) or tissue, additional host defenses act to limit and/or eliminate these pathogens. Initially, several primitive and relatively nonspecific host defenses act to contain the nidus of infection, which may include microbes as well as debris, devitalized tissue, and foreign bodies, depending on the nature of the injury. These defenses include the physical barrier of the tissue itself, as well as the capacity of proteins, such as lactoferrin and transferrin to sequester the critical microbial growth factor iron, thereby limiting microbial growth. In addition, fibrinogen within the inflammatory fluid has the ability to trap large numbers of microbes during the process in which it polymerizes into fibrin. Within the peritoneal cavity, unique host defenses exist, including a diaphragmatic pumping mechanism whereby particles, including microbes within peritoneal fluid are expunged from the abdominal cavity via specialized structures (stomata) on the undersurface of the diaphragm that lead to thoracic lymphatic channels. Concurrently, containment by the omentum, the so-called “gatekeeper” of the abdomen and intestinal ileus, serves to wall off infections. However, the latter processes and fibrin trapping have a high likelihood of contributing to the formation of an intra-abdominal abscess.

Microbes also immediately encounter a series of host defense mechanisms that reside within the vast majority of tissues of the body. These include resident macrophages and low levels of complement (C) proteins and immunoglobulins (e.g., antibodies).¹⁰ The response in macrophages is initiated by genome-encoded pattern recognition receptors which respond to invading microbes. With exposure to a foreign organism, these receptors recognize microbial pathogen-associated molecular patterns (PAMPs) and endogenous danger-associated molecular patterns (DAMPs). Toll-like receptors (TLRs) are one well-defined example of a PAMP that plays an important role in pathogen signaling.¹¹ Resident macrophages secrete a wide array of substances in response to the above-mentioned processes, some of which appear to regulate the cellular components of the host defense response. This results in recruitment and proliferation of inflammatory cells. Macrophage cytokine synthesis is upregulated. Secretion of tumor necrosis factor- α (TNF- α), of interleukins (IL)-1 β , 6, and 8; and of gamma interferon (IFN- γ) occurs within the tissue milieu, and, depending on the magnitude of the host defense response, the systemic circulation.¹² Concurrently, a counterregulatory response is initiated consisting of binding protein (TNF-BP), cytokine receptor antagonists (e.g., IL-1ra), and anti-inflammatory cytokines (IL-4 and IL-10).

The interaction of microbes with these first-line host defenses leads to microbial opsonization (C1q, C3bi, and IgFc), phagocytosis, and both extracellular (C5b6-9 membrane attack complex) and intracellular microbial destruction (via cellular ingestion into phagocytic vacuoles). Concurrently, the classical and alternate complement pathways are activated both via direct contact with and via IgM>IgG binding to microbes, leading to the release of a number of different complement protein fragments (C3a, C4a, C5a) that are biologically active, acting to markedly enhance vascular permeability. Bacterial cell wall components and a variety of enzymes that are expelled from

leukocyte phagocytic vacuoles during microbial phagocytosis and killing act in this capacity as well.

Simultaneously, the release of substances to which polymorphonuclear leukocytes (PMNs) in the bloodstream are attracted takes place. These consist of C5a, microbial cell wall peptides containing *N*-formyl-methionine, and macrophage secretion of cytokines such as IL-8. This process of host defense recruitment leads to further influx of inflammatory fluid into the area of incipient infection, and is accompanied by diapedesis of large numbers of PMNs, a process that begins within several minutes and may peak within hours or days. The magnitude of the response and eventual outcome generally are related to several factors: (a) the initial number of microbes, (b) the rate of microbial proliferation in relation to containment and killing by host defenses, (c) microbial virulence, and (d) the potency of host defenses. In regard to the latter, drugs or disease states that diminish any or multiple components of host defenses are associated with higher rates and potentially more grave infections.

Definitions

Several possible outcomes can occur subsequent to microbial invasion and the interaction of microbes with resident and recruited host defenses: (a) eradication, (b) containment, often leading to the presence of purulence—the hallmark of chronic infections (e.g., a furuncle in the skin and soft tissue or abscess within the parenchyma of an organ or potential space), (c) locoregional infection (cellulitis, lymphangitis, and aggressive soft tissue infection) with or without distant spread of infection (metastatic abscess), or (d) systemic infection (bacteremia or fungemia). Obviously, the latter represents the failure of resident and recruited host defenses at the local level, and is associated with significant morbidity and mortality in the clinical setting. In addition, it is not uncommon that disease progression occurs such that serious locoregional infection is associated with concurrent systemic infection. A chronic abscess also may intermittently drain and/or be associated with bacteremia.

Infection is defined by the presence of microorganisms in host tissue or the bloodstream. At the site of infection the classic findings of rubor, calor, and dolor in areas such as the skin or subcutaneous tissue are common. Most infections in normal individuals with intact host defenses are associated with these local manifestations, plus systemic manifestations such as elevated temperature, elevated white blood cell (WBC) count, tachycardia, or tachypnea. The systemic manifestations noted previously comprise the *systemic inflammatory response syndrome* (SIRS). A documented or suspected infection with some of the findings of SIRS define *sepsis*.¹³

SIRS can be caused by a variety of disease processes, including pancreatitis, polytrauma, malignancy, transfusion reaction, as well as infection (Fig. 6-1). There are a variety of systemic manifestations of infection, with the classic factors of fever, tachycardia, and tachypnea, broadened to include a variety of other variables (Table 6-1).¹³ Sepsis (SIRS caused by infection) is mediated by the production of a cascade of pro-inflammatory mediators produced in response to exposure to microbial products. These products include lipopolysaccharide (endotoxin, LPS) derived from Gram-negative organisms; peptidoglycans and teichoic acids from gram-positive organisms; many different microbial cell wall components, such as mannan from yeast and fungi; and many others.

Severe sepsis is characterized as sepsis (defined previously) combined with the presence of new-onset organ failure.

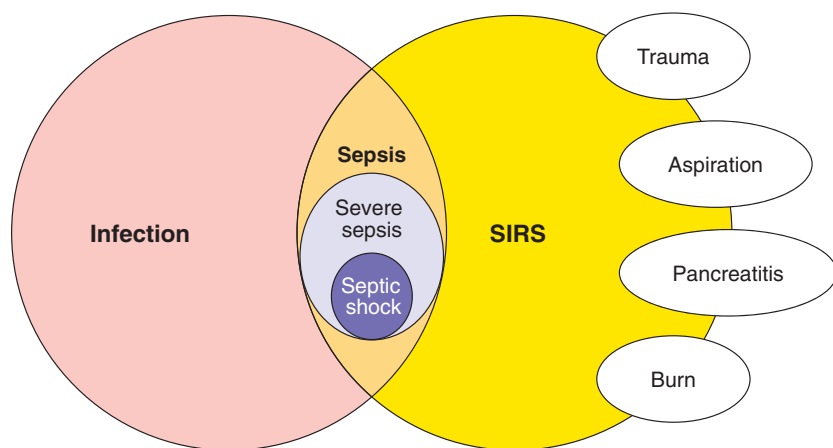


Figure 6-1. Relationship between infection and systemic inflammatory response syndrome (SIRS). Sepsis is the presence both of infection and the systemic inflammatory response, shown here as the intersection of these two areas. Other conditions may cause SIRS as well (trauma, aspiration, etc.). Severe sepsis (and septic shock) are both subsets of sepsis.

Severe sepsis is the most common cause of death in noncoronary critical care units and the 11th most common cause of death overall in the United States, with a mortality rate of 10.3 cases/100,000 population in 2010.¹⁴ A number of organ dysfunction scoring systems have been described.^{15,16,17} With

respect to clinical criteria, a patient with sepsis and the need for ventilatory support, with oliguria unresponsive to aggressive fluid resuscitation, or with hypotension requiring vasopressors should be considered to have developed severe sepsis. *Septic shock* is a state of acute circulatory failure identified by the presence of persistent arterial hypotension (systolic blood pressure <90 mm Hg) despite adequate fluid resuscitation, without other identifiable causes. Septic shock is the most severe manifestation of infection, occurring in approximately 40% of patients with severe sepsis; it has an attendant mortality rate of 30% to 66%.^{18,19}

While classification of severity of shock has been successful in driving efforts to improve patient outcomes, staging of sepsis by other patient characteristics remains in its infancy. The impetus for development of such a scheme is related to the heterogeneity of the patient population developing sepsis, an example of which would include two patients, both in the intensive care unit (ICU), who develop criteria consistent with septic shock. While both have infection and sepsis-associated hypotension, one might expect a different outcome in a young, healthy patient who develops urosepsis than in an elderly, immunosuppressed lung transplant recipient who develops invasive fungal infection. One schema for providing such a classification is the predisposition, infection, response and organ failure (PIRO) classification.²⁰ This scheme has borrowed from the tumor-node-metastasis staging scheme developed for oncology. The PIRO staging system stratifies patients based on their predisposing conditions (P), the nature and extent of the infection (I), the nature and magnitude of the host response (R), and the degree of concomitant organ dysfunction (O). Clinical trials using this classification system have confirmed the validity of this concept.^{21, 22}

Table 6-1

Criteria for systemic inflammatory response syndrome (SIRS)

General variables

Fever (core temp >38.3°C)
Hypothermia (core temp <36°C)
Heart rate >90 bpm
Tachypnea

Altered mental status

Significant edema or positive fluid balance (>20 mL/kg over 24 h)
Hyperglycemia in the absence of diabetes

Inflammatory variables

Leukocytosis (WBC >12,000)
Leukopenia (WBC <4000)
Bandemia (>10% band forms)
Plasma C-reactive protein >2 s.d. above normal value
Plasma procalcitonin >2 s.d. above normal value

Hemodynamic variables

Arterial hypotension (SBP <90 mm Hg, MAP <70, or SBP decrease >40 mm Hg)

Organ dysfunction variables

Arterial hypoxemia
Acute oliguria
Creatinine increase
Coagulation abnormalities
Ileus
Thrombocytopenia
Hyperbilirubinemia

Tissue perfusion variables

Hyperlactatemia
Decreased capillary filling

bpm = beats per minute; MAP = mean arterial pressure; SBP = systolic blood pressure; s.d. = standard deviations; Svo₂ = venous oxygen saturation; WBC = white blood cell count.

MICROBIOLOGY OF INFECTIOUS AGENTS

A partial list of common pathogens that cause infections in surgical patients is provided in Table 6-2.

Bacteria

Bacteria are responsible for the majority of surgical infections. Specific species are identified using Gram's stain and growth characteristics on specific media. The Gram's stain is an important evaluation that allows rapid classification of bacteria by color. This color is related to the staining characteristics of the bacterial cell wall: gram-positive bacteria stain blue and Gram-negative bacteria stain red. Bacteria are classified based upon

Table 6-2

Common Pathogens in Surgical Patients

Gram-positive aerobic cocci

Staphylococcus aureus
Staphylococcus epidermidis
Streptococcus pyogenes
Streptococcus pneumoniae
Enterococcus faecium, *E. faecalis*

Gram-negative aerobic bacilli

Escherichia coli
Haemophilus influenzae
Klebsiella pneumoniae
Proteus mirabilis
Enterobacter cloacae, *E. aerogenes*
Serratia marcescens
Acinetobacter calcoaceticus
Citrobacter freundii
Pseudomonas aeruginosa
Xanthomonas maltophilia

Anaerobes

Gram-positive
Clostridium difficile
Clostridium perfringens, *C. tetani*, *C. septicum*
Peptostreptococcus spp.
 Gram-negative
Bacteroides fragilis
Fusobacterium spp.

Other bacteria

Mycobacterium avium-intracellulare
Mycobacterium tuberculosis
Nocardia asteroides
Legionella pneumophila
Listeria monocytogenes

Fungi

Aspergillus fumigatus, *A. niger*, *A. terreus*, *A. flavus*
Blastomyces dermatitidis
Candida albicans
Candida glabrata, *C. parapsilosis*, *C. krusei*
Coccidioides immitis
Cryptococcus neoformans
Histoplasma capsulatum
Mucor/Rhizopus

Viruses

Cytomegalovirus
 Epstein-Barr virus
 Hepatitis A, B, C viruses
 Herpes simplex virus
 Human immunodeficiency virus
 Varicella zoster virus

a number of additional characteristics, including morphology (cocci and bacilli), the pattern of division (e.g., single organisms, groups of organisms in pairs [diplococci], clusters [staphylococci], and chains [streptococci]), and the presence and location of spores.

Gram-positive bacteria that frequently cause infections in surgical patients include aerobic skin commensals (*Staphylococcus*

aureus and *epidermidis* and *Streptococcus pyogenes*) and enteric organisms such as *Enterococcus faecalis* and *faecium*. Aerobic skin commensals cause a large percentage of surgical site infections (SSIs), either alone or in conjunction with other pathogens; enterococci can cause nosocomial infections (urinary tract infections [UTIs] and bacteremia) in immunocompromised or chronically ill patients, but are of relatively low virulence in healthy individuals.

There are many pathogenic Gram-negative bacterial species that are capable of causing infection in surgical patients. Most Gram-negative organisms of interest to the surgeon are bacilli belonging to the family Enterobacteriaceae, including *Escherichia coli*, *Klebsiella pneumoniae*, *Serratia marcescens*, and *Enterobacter*, *Citrobacter*, and *Acinetobacter* spp. Other Gram-negative bacilli of note include *Pseudomonas* spp., including *Pseudomonas aeruginosa* and *fluorescens* and *Xanthomonas* spp.

Anaerobic organisms are unable to grow or divide poorly in air, as most do not possess the enzyme catalase, which allows for metabolism of reactive oxygen species. Anaerobes are the predominant indigenous flora in many areas of the human body, with the particular species being dependent on the site. For example, *Propionibacterium acnes* and other species are a major component of the skin microflora and cause the infectious manifestation of acne. As noted previously, large numbers of anaerobes contribute to the microflora of the oropharynx and colon.

Infection due to *Mycobacterium tuberculosis* was once one of the most common causes of death in Europe, causing one in four deaths in the seventeenth and eighteenth centuries. In the nineteenth and twentieth centuries, thoracic surgical intervention was often required for severe pulmonary disease, now an increasingly uncommon occurrence in developed countries. This organism and other related organisms (*M avium-intracellulare* and *M leprae*) are known as acid-fast bacilli. Other acid-fast bacilli include *Nocardia* spp. These organisms typically are slow-growing, sometimes necessitating observation in culture for weeks to months prior to final identification, although deoxyribonucleic acid (DNA)-based analysis is increasingly available to provide a means for preliminary, rapid detection.

Fungi

Fungi typically are identified by use of special stains (e.g., potassium hydroxide (KOH), India ink, methenamine silver, or Giemsa). Initial identification is assisted by observation of the form of branching and septation in stained specimens or in culture. Final identification is based on growth characteristics in special media, similar to bacteria, as well as on the capacity for growth at a different temperature (25°C vs. 37°C). Fungi of relevance to surgeons include those that cause nosocomial infections in surgical patients as part of polymicrobial infections or fungemia (e.g., *Candida albicans* and related species), rare causes of aggressive soft tissue infections (e.g., *Mucor*, *Rhizopus*, and *Absidia* spp.), and so-called opportunistic pathogens that cause infection in the immunocompromised host (e.g., *Aspergillus fumigatus*, *niger*, *terreus*, and other spp., *Blastomyces dermatitidis*, *Coccidioides immitis*, and *Cryptococcus neoformans*). Agents currently available for antifungal therapy are described in Table 6-3.

Viruses

Due to their small size and necessity for growth within cells, viruses are difficult to culture, requiring a longer time than is typically optimal for clinical decision making. Previously, viral

Table 6-3

Antifungal agents and their characteristics

ANTIFUNGAL	ADVANTAGES	DISADVANTAGES
Amphotericin B	Broad-spectrum, inexpensive	Renal toxicity, premeds, IV only
Liposomal Amphotericin B	Broad-spectrum	Expensive, IV only, renal toxicity
<i>Azoles</i>		
Fluconazole	IV and PO availability	Narrow-spectrum, drug interactions
Itraconazole	IV and PO availability	Narrow spectrum, no CSF penetration Drug interactions, decreased cardiac contractility
Posaconazole	Broad-spectrum, zygomycete activity	PO only
Voriconazole	IV and PO availability, broad-spectrum	IV diluent accumulates in renal failure (PO) Visual disturbances
<i>Echinocandins</i>		
Anidulafungin, caspofungin, micafungin	Broad-spectrum	IV only, poor CNS penetration

infection was identified by indirect means (i.e., the host antibody response). Recent advances in technology have allowed for the identification of the presence of viral DNA or ribonucleic acid (RNA) using methods such as polymerase chain reaction. Similarly to many fungal infections, most clinically relevant viral infections in surgical patients occur in the immunocompromised host, particularly those receiving immunosuppression to prevent rejection of a solid organ allograft. Relevant viruses include adenoviruses, cytomegalovirus, Epstein-Barr virus, herpes simplex virus, and varicella-zoster virus. Surgeons must be aware of the manifestations of hepatitis B and C virus, as well as human immunodeficiency virus infections, including their capacity to be transmitted to health care workers (see *General Principles* section). Prophylactic and therapeutic use of antiviral agents is discussed in Chap. 11.

PREVENTION AND TREATMENT OF SURGICAL INFECTIONS

General Principles

Maneuvers to diminish the presence of exogenous (surgeon and operating room environment) and endogenous (patient) microbes are termed *prophylaxis*, and consist of the use of mechanical, chemical, and antimicrobial modalities, or a combination of these methods.

As described previously, the host resident microflora of the skin (patient and surgeon) and other barrier surfaces represent a potential source of microbes that can invade the body during trauma, thermal injury, or elective or emergent surgical intervention. For this reason, operating room personnel are versed in mild mechanical exfoliation of the skin of the hands and forearms using antibacterial preparations, and the intraoperative aseptic technique is employed. Similarly, application of an antibacterial agent to the skin of the patient at the proposed operative site takes place prior to creating an incision. Also, if necessary, hair removal should take place using a clipper rather than a razor; the latter promotes overgrowth of skin microbes in small nicks and cuts. Dedicated use of these modalities clearly

has been shown to diminish the quantity of skin microflora, and although a direct correlation between praxis and reduced infection rates has not been demonstrated, comparison to infection rates prior to the use of antisepsis and sterile technique makes clear their utility and importance.

The aforementioned modalities are not capable of sterilizing the hands of the surgeon or the skin or epithelial surfaces of the patient, although the inoculum can be reduced considerably. Thus, entry through the skin, into the soft tissue, and into a body cavity or hollow viscus invariably is associated with the introduction of some degree of microbial contamination. For that reason, patients who undergo procedures that may be associated with the ingress of significant numbers of microbes (e.g., colonic resection) or in whom the consequences of any type of infection due to said process would be dire (e.g., prosthetic vascular graft infection) should receive an antimicrobial agent.

Source Control

The primary precept of surgical infectious disease therapy consists of drainage of all purulent material, débridement of all infected, devitalized tissue, and debris, and/or removal of foreign bodies at the site of infection, plus remediation of the underlying cause of infection.²³ A discrete, walled-off purulent fluid collection (i.e., an abscess) requires drainage via percutaneous drain insertion or an operative approach in which incision and drainage take place. An ongoing source of contamination (e.g., bowel perforation) or the presence of an aggressive, rapidly spreading infection (e.g., necrotizing soft tissue infection) invariably requires expedient, aggressive operative intervention, both to remove contaminated material and infected tissue (e.g., radical débridement or amputation) and to remove the initial cause of infection (e.g., bowel resection). Other treatment modalities such as antimicrobial agents, albeit critical, are of secondary importance to effective surgery with regard to treatment of surgical infections and overall outcome. Rarely, if ever, can an aggressive surgical infection be cured only by the administration of antibiotics, and never in the face of an ongoing source of contamination. Also, it has been repeatedly demonstrated that delay in operative intervention, whether due

to misdiagnosis or the need for additional diagnostic studies, is associated with increased morbidity and occasional mortality.²⁴

Appropriate Use of Antimicrobial Agents

A classification of antimicrobial agents, mechanisms of action, and spectrum of activity is shown in Table 6-4. *Prophylaxis* consists of the administration of an antimicrobial agent or agents prior to initiation of certain specific types of surgical procedures in order to reduce the number of microbes that enter the tissue or body cavity. Agents are selected according to their activity against microbes likely to be present at the surgical site, based on knowledge of host microflora. For example, patients undergoing elective colorectal surgery should receive antimicrobial prophylaxis directed against skin flora, gram negative aerobes, and anaerobic bacteria. There are a wide variety of agents that meet these criteria with recently published guidelines.²⁵

By definition, prophylaxis is limited to the time prior to and during the operative procedure; in the vast majority of cases only a single dose of antibiotic is required, and only for certain types of procedures (see Surgical Site Infections). However, patients who undergo complex, prolonged procedures in which the duration of the operation exceeds the serum drug half-life should receive an additional dose or doses of the antimicrobial agent.²⁵ There is no evidence that administration of postoperative doses of an antimicrobial agent provides additional benefit, and this practice should be discouraged, as it is costly and is associated with increased rates of microbial drug resistance. Guidelines for prophylaxis are provided in Table 6-5.

Empiric therapy comprises the use of an antimicrobial agent or agents when the risk of a surgical infection is high, based on the underlying disease process (e.g., ruptured appendicitis), or when significant contamination during surgery has occurred (e.g., inadequate bowel preparation or considerable spillage of colon contents). Obviously, prophylaxis merges into empirical therapy in situations in which the risk of infection increases markedly because of intraoperative findings. Empirical therapy also often is employed in critically ill patients in whom a potential site of infection has been identified and severe sepsis or septic shock occurs. Invariably, empirical therapy should be limited to a short course of drug (3 to 5 days), and should be curtailed as soon as possible based on microbiologic data (i.e., absence of positive cultures) coupled with improvements in the clinical course of the patient.

Similarly, empirical therapy merges into therapy of established infection in some patients as well. However, among surgical patients, the manner in which therapy is employed, particularly in relation to the use of microbiologic data (culture and antibiotic sensitivity patterns), differs depending on whether the infection is monomicrobial or polymicrobial. Monomicrobial infections frequently are nosocomial infections occurring in postoperative patients, such as UTIs, pneumonia, or bacteremia. Evidence of systemic inflammatory response syndrome (fever, tachycardia, tachypnea, or elevated leukocyte count) in such individuals, coupled with evidence of local infection (e.g., an infiltrate on chest roentgenogram plus a positive Gram's stain in bronchoalveolar lavage samples) should lead the surgeon to initiate empirical antibiotic therapy. An appropriate approach to antimicrobial treatment involves de-escalation therapy, where initial antimicrobial selection is broad, with a later narrowing of agents based on patient response and culture results. Initial drug selection must be based on initial evidence (Gram-positive vs.

Gram-negative microbes, yeast), coupled with institutional and unit-specific drug sensitivity patterns. It is important to ensure that antimicrobial coverage chosen is adequate, since delay in appropriate antibiotic treatment has been shown to be associated with significant increases in mortality. A critical component of this approach is appropriate collection of culture specimens to allow for thorough analysis, since within 48 to 72 hours, culture and sensitivity reports will allow refinement of the antibiotic regimen to select the most efficacious agent. The clinical course of the patient is monitored closely, and in some cases (e.g., UTI) follow-up studies (urine culture) should be obtained after completion of therapy.

Although the primary therapeutic modality to treat polymicrobial surgical infections is source control as delineated previously, antimicrobial agents play an important role as well. Culture results are of lesser importance in managing these types of infections, as it has been repeatedly demonstrated that only a limited cadre of microbes predominate in the established infection, selected from a large number present at the time of initial contamination. Invariably it is difficult to identify all microbes that comprise the initial polymicrobial inoculum. For this reason, the antibiotic regimen should not be modified solely on the basis of culture information, as it is less important than the clinical course of the patient. For example, patients who undergo appendectomy for gangrenous, perforated appendicitis, or bowel resection for intestinal perforation, should receive an antimicrobial agent or agents directed against aerobes and anaerobes for 3 to 5 days, occasionally longer. If the patient regains bowel function during this time, conversion from an intravenous to an oral regimen (e.g., ciprofloxacin plus metronidazole) can occur. This is safe, and may facilitate earlier discharge.

A survey of several decades of clinical trials examining the effect of antimicrobial agent selection on the treatment of intra-abdominal infection revealed striking similarities in outcome among regimens that possessed aerobic and anaerobic activity (~10% to 30% failure rates): most failures could not be attributed to antibiotic selection, but rather were due to the inability to achieve effective source control.²⁶

Duration of antibiotic administration should be decided at the time the drug regimen is prescribed. As mentioned previously, prophylaxis is limited to a single dose administered immediately prior to creating the incision. Empiric therapy should be limited to 3 to 5 days or less, and should be curtailed if the presence of a local site or systemic infection is not revealed.²⁷ In fact, prolonged use of empirical antibiotic therapy in culture-negative critically ill patients is associated with increased mortality, highlighting the need to discontinue therapy when there is no proven evidence of infection.²⁸

Therapy for monomicrobial infections follows standard guidelines: 3 to 5 days for UTIs, 7 to 10 days for pneumonia, and 7 to 14 days for bacteremia. Longer courses of therapy in this setting do not result in improved care and are associated with increased risk of superinfection by resistant organisms.^{29,30} There is some evidence that measuring and monitoring serum procalcitonin trends in the setting of infection allows earlier cessation of antibiotics without decrement in the rate of clinical cure.³¹ Antibiotic therapy for osteomyelitis, endocarditis, or prosthetic infections in which it is hazardous to remove the device consists of prolonged courses of an antibiotic or several agents in combination for 6 to 12 weeks. The specific agents are selected based on analysis of the degree to which the organism is killed in vitro using the minimum inhibitory concentration

Table 6-4

Antimicrobial agents

ANTIBIOTIC CLASS, GENERIC NAME	TRADE NAME	MECHANISM OF ACTION	ORGANISM								
			S. PYOGENES	MSSA	MRSA	S. EPIDERMIDIS	ENTEROCOCCUS	VRE	E. COLI	P. AERUGINOSA	ANAEROBES
Penicillins		Cell wall synthesis inhibitors (bind penicillin-binding protein)									
Penicillin G			1	0	0	0	+/-	0	0	0	1
Nafcillin	Nallpen, Unipen		1	1	0	+/-	0	0	0	0	0
Piperacillin	Pipracil		1	0	0	0	+/-	0	1	1	+/-
Penicillin/beta lactamase inhibitor combinations		Cell wall synthesis inhibitors/beta lactamase inhibitors									
Ampicillin-sulbactam	Unasyn		1	1	0	+/-	1	+/-	1	0	1
Ticarcillin-clavulanate	Timentin		1	1	0	+/-	+/-	0	1	1	1
Piperacillin-tazobactam	Zosyn		1	1	0	1	+/-	0	1	1	1
First-generation cephalosporins		Cell wall synthesis inhibitors (bind penicillin-binding protein)									
Cefazolin, cephalexin	Ancef, Keflex		1	1	0	+/-	0	0	1	0	0
Second-generation cephalosporins		Cell wall synthesis inhibitors (bind penicillin-binding protein)									
Cefoxitin	Mefoxin		1	1	0	+/-	0	0	1	0	1
Cefotetan	Cefotan		1	1	0	+/-	0	0	1	0	1
Cefuroxime	Ceftin		1	1	0	+/-	0	0	1	0	0
Third- and fourth-generation cephalosporins		Cell wall synthesis inhibitors (bind penicillin-binding protein)									

(Continued)

Table 6-4

Antimicrobial agents (continued)

ANTIBIOTIC CLASS, GENERIC NAME	TRADE NAME	MECHANISM OF ACTION	ORGANISM								
			S. PYOGENES	MSSA	MRSA	S. EPIDERMIDIS	ENTEROCOCCUS	VRE	E. COLI	P. AERUGINOSA	ANAEROBES
Ceftriaxone	Rocephin		1	1	0	+/-	0	0	1	0	0
Ceftazidime	Fortaz		1	+/-	0	+/-	0	0	1	1	0
Cefepime	Maxipime		1	1	0	+/-	0	0	1	1	0
Cefotaxime	Cefotaxime		1	1	0	+/-	0	0	1	+/-	0
ceftaroline	Teflaro		1	1	1	1	0	0	1	0	0
Carbapenems		Cell wall synthesis inhibitors (bind penicillin-binding protein)									
Imipenem-cilastatin	Primaxin		1	1	0	1	+/-	0	1	1	1
Meropenem	Merrem		1	1	0	1	0	0	1	1	1
Ertapenem	Invanz		1	1	0	1	0	0	1	+/-	1
Aztreonam	Azactam		0	0	0	0	0	0	1	1	0
Aminoglycosides		Alteration of cell membrane, binding and inhibition of 30S ribosomal unit									
Gentamicin			0	1	0	+/-	1	0	1	1	0
Tobramycin, amikacin			0	1	0	+/-	0	0	1	1	0
Fluoroquinolones		Inhibit topoisomerase II and IV (DNA synthesis inhibition)									
Ciprofloxacin	Cipro		+/-	1	0	1	0	0	1	1	0
Levofloxacin	Levaquin		1	1	0	1	0	0	1	+/-	0
Glycopeptides		Cell wall synthesis inhibition (peptidoglycan synthesis inhibition)								0	0
Vancomycin	Vancocin		1	1	1	1	1	0	0	0	0

Quinupristin-Dalfopristin	Synercid	Inhibits 2 sites on 50S ribosome (protein synthesis inhibition)	1	1	1	1	1	1	0	0	+/-
Linezolid	Zyvox	Inhibits 50S ribosomal activity (protein synthesis inhibition)	1	1	1	1	1	1	0	0	+/-
Daptomycin	Cubicin	Binds bacterial membrane, results in depolarization, lysis	1	1	1	1	1	1	0	0	0
Rifampin		Inhibits DNA-dependent RNA polymerase	1	1	1	1	+/-	0	0	0	0
Clindamycin	Cleocin	Inhibits 50S ribosomal activity (protein synthesis inhibition)	1	1	0	0	0	0	0	0	1
Metronidazole	Flagyl	Production of toxic intermediates (free radical production)	0	0	0	0	0	0	0	0	1
Macrolides		Inhibit 50S ribosomal activity (protein synthesis inhibition)									
Erythromycin			1	+/-	0	+/-	0	0	0	0	0
Azithromycin	Zithromax		1	1	0	0	0	0	0	0	0
Clarithromycin	Biaxin		1	1	0	0	0	0	0	0	0
Trimethoprim-sulfamethoxazole	Bactrim, Septra	Inhibits sequential steps of folate metabolism	+/-	1	0	+/-	0	0	1	0	0
Tetracyclines		Bind 30S ribosomal unit (protein synthesis inhibition)									
Minocycline	Minocin		1	1	0	0	0	0	0	0	+/-
Doxycycline	Vibromycin		1	+/-	0	0	0	0	1	0	+/-
Tigacycline	Tygacil	1	1	1	1	1	1	1	1	0	1

E coli = *Escherichia coli*; MRSA = methicillin-resistant *Staphylococcus aureus*; MSSA = methicillin-sensitive *Staphylococcus aureus*; *P aeruginosa* = *Pseudomonas aeruginosa*; *S epidermidis* = *Staphylococcus epidermidis*; *S pyogenes* = *Streptococcus pyogenes*; VRE = vancomycin-resistant enterococcus.

1 = Reliable activity; +/- = variable activity; 0 = no activity.

The sensitivities presented are generalizations. The clinician should confirm sensitivity patterns at the locale where the patient is being treated since these patterns may vary widely depending on location.

Table 6-5

Prophylactic use of antibiotics (adapted from ref 25)

SITE	ANTIBIOTIC	ALTERNATIVE (E.G., PENICILLIN ALLERGIC)
Cardiovascular surgery	Cefazolin, cefuroxime	Vancomycin, clindamycin
Gastroduodenal area; small intestine, nonobstructed	Cefazolin	Clindamycin or vancomycin + aminoglycoside or aztreonam or fluoroquinolone
Biliary tract: open procedure, laparoscopic high risk	Cefazolin, cefoxitin, cefotetan, ceftriaxone, ampicillin-sulbactam,	Clindamycin or vancomycin + aminoglycoside or aztreonam or fluoroquinolone Metronidazole + aminoglycoside or fluoroquinolone
Biliary tract: laparoscopic low risk	None	none
Appendectomy, uncomplicated	Cefoxitin, cefotetan, cefazolin + metronidazole	Clindamycin + aminoglycoside or aztreonam or fluoroquinolone Metronidazole + aminoglycoside or fluoroquinolone
Colorectal surgery, obstructed small intestine	Cefazolin or ceftriaxone plus metronidazole, Ertapenem, cefoxitin, cefotetan, ampicillin-sulbactam	Clindamycin + aminoglycoside or aztreonam or fluoroquinolone, metronidazole + aminoglycoside or fluoroquinolone
Head and neck; clean contaminated	Cefazolin or cefuroxime + metronidazole, ampicillin-sulbactam	clindamycin
Neurosurgical procedures	Cefazolin	Clindamycin, Vancomycin
Orthopedic surgery	Cefazolin, ceftriaxone	Clindamycin, Vancomycin
Breast, hernia	Cefazolin	Clindamycin, Vancomycin

(MIC) of a standard pure inoculum of 10^5 CFU/mL of the organism isolated from the site of infection or bloodstream. Sensitivities are reported in relation to the achievable blood level of each antibiotic in a panel of agents. The least toxic, least expensive agent to which the organism is most sensitive should be selected, although the latter parameter is of paramount importance. Serious or recrudescence infection may require therapy with two or more agents, particularly if a multidrug-resistant pathogen is causative, limiting therapeutic options to drugs to which the organism is only moderately sensitive. Commonly an agent may be administered intravenously for 1 to 2 weeks, following which the treatment course is completed with an oral drug. However, this should only be undertaken in patients who demonstrate progressive clinical improvement, and the oral agent should be capable of achieving high serum levels as well (e.g., fluoroquinolones).

The majority of studies examining the optimal duration of antibiotic therapy for the treatment of polymicrobial infection have focused on patients who develop peritonitis. CoGeNT data exist to support the contention that satisfactory outcomes are achieved with 12 to 24 hours of therapy for penetrating gastrointestinal trauma in the absence of extensive contamination, 3 to 5 days of therapy for perforated or gangrenous appendicitis, 5 to 7 days of therapy for treatment of peritoneal soilage due to a perforated viscus with moderate degrees of contamination, and 7 to 14 days of therapy to adjunctively treat extensive peritoneal soilage (e.g., feculent peritonitis) or that occurring in the immunosuppressed host.³² It bears repeating that the eventual outcome is more closely linked to the ability of the surgeon to achieve effective source control than to the duration of antibiotic administration. One small randomized trial has reported

similar outcomes of 3 day vs. standard duration therapy in secondary microbial peritonitis.³³

In the later phases of postoperative antibiotic treatment of serious intra-abdominal infection, the absence of an elevated white blood cell (WBC) count, lack of band forms of PMNs on peripheral smear, and lack of fever ($<100.5^\circ\text{F}$) provide close to complete assurance that infection has been eradicated.³⁴ Under these circumstances, antibiotics can be discontinued with impunity. However, the presence of one or more of these indicators does not mandate continuing antibiotics or altering the antibiotic(s) administered. Rather, a search for an extra-abdominal source of infection or a residual or ongoing source of intra-abdominal infection (e.g., abscess or leaking anastomosis) should be sought, the latter mandating maneuvers to effect source control.

Allergy to antimicrobial agents must be considered prior to prescribing them. First, it is important to ascertain whether a patient has had any type of allergic reaction in association with administration of a particular antibiotic. However, one should take care to ensure that the purported reaction consists of true allergic symptoms and signs, such as urticaria, bronchospasm, or other similar manifestations, rather than indigestion or nausea. Penicillin allergy is quite common, the reported incidence ranging from 0.7% to 10%. Although avoiding the use of any beta-lactam drug is appropriate in patients who manifest significant allergic reactions to penicillins, the incidence of cross-reactivity appears low for all related agents, with 1% cross-reactivity for carbapenems,³⁵ 5% to 7% cross-reactivity for cephalosporins, and extremely small or nonexistent cross-reactivity for monobactams.

Severe allergic manifestations to a specific class of agents, such as anaphylaxis, generally preclude the use of any agents in

that class, except under circumstances in which use of a certain drug represents a lifesaving measure. In some centers, patients undergo intradermal testing using a dilute solution of a particular antibiotic to determine whether a severe allergic reaction would be elicited by parenteral administration. A pathway, including such intradermal testing, has been effective in reduction of vancomycin use to 16% in surgical patients with reported allergy to penicillin.³⁶ This type of testing is rarely employed because it is simpler to select an alternative class of agent. Should administration of a specific agent to which the patient is allergic become necessary, desensitization using progressively higher doses of antibiotic can be undertaken, providing the initial testing does not cause severe allergic manifestations.

Misuse of antimicrobial agents is rampant in both the inpatient and outpatient setting, and is associated with an enormous financial impact on health care costs, adverse reactions due to drug toxicity and allergy, the occurrence of new infections such as *Clostridium difficile* colitis, and the development of multiagent drug resistance among nosocomial pathogens. Each of these factors has been directly correlated with overall drug administration. It has been estimated that in the United States, in excess of \$20 billion is spent on antibiotics each year, and the appearance of so-called “super bugs”—microbes sensitive to few if any agents—has been sobering.³⁷ The responsible practitioner limits prophylaxis to the period during the operative procedure, does not convert prophylaxis into empirical therapy except under well-defined conditions, sets the duration of antibiotic therapy from the outset, curtails antibiotic administration when clinical and microbiologic evidence does not support the presence of an infection, and limits therapy to a short course in every possible instance. Prolonged treatment associated with drains and tubes has not been shown to be beneficial.

INFECTIONS OF SIGNIFICANCE IN SURGICAL PATIENTS

Surgical Site Infections

Surgical site infections (SSIs) are infections of the tissues, organs, or spaces exposed by surgeons during performance of an invasive procedure. SSIs are classified into incisional and organ/space infections, and the former are further subclassified into superficial (limited to skin and subcutaneous tissue) and deep incisional categories.^{38,39} The development of SSIs is related to three factors: (a) the degree of microbial contamination of the wound during surgery, (b) the duration of the procedure, and (c) host factors such as diabetes, malnutrition, obesity, immune suppression, and a number of other underlying disease states. Table 6-6 lists risk factors for development of SSIs. By definition, an incisional SSI has occurred if a surgical wound drains purulent material or if the surgeon judges it to be infected and opens it.

Surgical wounds are classified based on the presumed magnitude of the bacterial load at the time of surgery (Table 6-7).⁴⁰ *Clean wounds* (class I) include those in which no infection is present; only skin microflora potentially contaminate the wound, and no hollow viscus that contains microbes is entered. Class I D wounds are similar except that a prosthetic device (e.g., mesh or valve) is inserted. *Clean/contaminated wounds* (class II) include those in which a hollow viscus such as the respiratory, alimentary, or genitourinary tracts with indigenous

Table 6-6

Risk factors for development of surgical site infections

Patient factors

- Older age
- Immunosuppression
- Obesity
- Diabetes mellitus
- Chronic inflammatory process
- Malnutrition
- Smoking
- Renal failure
- Peripheral vascular disease
- Anemia
- Radiation
- Chronic skin disease
- Carrier state (e.g., chronic *Staphylococcus* carriage)
- Recent operation

Local factors

- Open compared to laparoscopic surgery
- Poor skin preparation
- Contamination of instruments
- Inadequate antibiotic prophylaxis
- Prolonged procedure
- Local tissue necrosis
- Blood transfusion
- Hypoxia, hypothermia

Microbial factors

- Prolonged hospitalization (leading to nosocomial organisms)
- Toxin secretion
- Resistance to clearance (e.g., capsule formation)

bacterial flora is opened under controlled circumstances without significant spillage of contents.

While elective colorectal cases have classically been included as class II cases, a number of studies in the last decade have documented higher SSI rates (9% to 25%).⁴¹⁻⁴³ One study identified two-thirds of infections presenting after discharge from hospital, highlighting the need for careful follow-up of these patients.⁴¹ Infection is also more common in cases involving entry into the rectal space.⁴² In a recent single center quality improvement study using a multidisciplinary approach, one group of clinicians has demonstrated the ability to decrease SSI from 9.8% to 4.0%.⁴³

Contaminated wounds (class III) include open accidental wounds encountered early after injury, those with extensive introduction of bacteria into a normally sterile area of the body due to major breaks in sterile technique (e.g., open cardiac massage), gross spillage of viscus contents such as from the intestine, or incision through inflamed, albeit nonpurulent tissue. *Dirty wounds* (class IV) include traumatic wounds in which a significant delay in treatment has occurred and in which necrotic tissue is present, those created in the presence of overt infection as evidenced by the presence of purulent material, and those created to access a perforated viscus accompanied by a high degree of contamination. The microbiology of SSIs is reflective of the initial host microflora such that SSIs following creation of a class I wound are invariable, due solely to skin microbes found

Table 6-7

Wound class, representative procedures, and expected infection rates

WOUND CLASS	EXAMPLES OF CASES	EXPECTED INFECTION RATES
Clean (class I)	Hernia repair, breast biopsy specimen	1%–2%
Clean/contaminated (class II)	Cholecystectomy, elective GI surgery (not colon)	2.1%–9.5%
Clean/contaminated (class II)	Colorectal surgery	4%–14%
Contaminated (class III)	Penetrating abdominal trauma, large tissue injury, enterotomy during bowel obstruction	3.4%–13.2%
Dirty (class IV)	Perforated diverticulitis, necrotizing soft tissue infections	3.1%–12.8%

on that portion of the body, while SSIs subsequent to a class II wound created for the purpose of elective colon resection may be caused by either skin microbes or colonic microflora, or both.

In the United States, hospitals are required to conduct surveillance for the development of SSIs for a period of 30 days after the operative procedure.⁴⁴ Such surveillance has been associated with greater awareness and a reduction in SSI rates, probably in large part based upon the impact of observation and promotion of adherence to appropriate care standards. Beginning in 2012, all hospitals receiving reimbursement from the Center for Medicare and Medicaid Services are required to report SSIs.

A recent refinement of risk indexes has been implemented through the National Healthcare Safety Network, a secure, web-based system of surveillance utilized by the Centers for Disease Control and Prevention for surveillance of health care associated infections. This refinement utilized data reported from 847 hospitals in nearly one million patients over a two-year period to develop procedure-specific risk indices for SSIs.⁴⁵

SSIs are associated with considerable morbidity and occasional lethality, as well as substantial health care costs and patient inconvenience and dissatisfaction.⁴⁶ For that reason, surgeons strive to avoid SSIs by using the maneuvers described in the previous section. Also, the use of prophylactic antibiotics may serve to reduce the incidence of SSI rates during certain types of procedures. For example, it is well accepted that a single

dose of an antimicrobial agent should be administered immediately prior to commencing surgery for class I D, II, III, and IV types of wounds. It seems reasonable that this practice should be extended to patients in any category with high National Nosocomial Infection Surveillance (NNIS) scores, although this remains to be proven. Thus, the utility of prophylactic antibiotics in reducing the rate of wound infection subsequent to clean surgery remains controversial, and these agents should not be employed under routine circumstances (e.g., in healthy young patients). However, because of the potential dire consequences of a wound infection after clean surgery in which prosthetic material is implanted into tissue, patients who undergo such procedures should receive a single preoperative dose of an antibiotic.

A number of health care organizations within the United States have become interested in evaluating performance of hospitals and physicians with respect to implementing processes that support delivery of standard of care. One major process of interest is reduction in SSIs, since the morbidity (and subsequent cost) of this complication is high. Several of these organizations are noted in Table 6-8. Appropriate guidelines in this area incorporating the principles discussed previously have been developed and disseminated.⁴⁷ However, observers have noted that adherence to these guidelines has been poor.⁴⁸ Most experts believe that better adherence to evidence-based practice recommendations and implementing systems of care

Table 6-8

Quality improvement organizations in the United States of interest to surgeons

ABBREVIATION	ORGANIZATION	WEBSITE
SCIP	Surgical Care Improvement Project	www.premierinc.com/safety/topics/scip/
NSQIP	National Surgical Quality Improvement Program	www.acsnsqip.org
IHI	Institute for Healthcare Improvement	www.ihl.org
CMS	Center for Medicare and Medicaid Services	www.cms.gov
NCQA	National Committee for Quality Assurance	www.ncqa.org
SIS	Surgical Infection Society	www.sisna.org
CDC	Centers for Disease Control and Prevention	www.cdc.gov/HAI/ssi/ssi.html

with redundant safeguards will result in reduction of surgical complications and better patient outcomes. More important, the Center for Medicare and Medicaid Services, the largest third party insurance payer in the United States, has required reporting by hospitals of many processes related to reduction of surgical infections, including appropriate use of perioperative antibiotics. This information, which is currently reported publicly by hospitals, has led to significant improvement in reported rates of these process measures. However, the effect of this approach on the incidence of SSIs is not known at this time.

Surgical management of the wound also is a critical determinant of the propensity to develop a SSI. In healthy individuals, class I and II wounds may be closed primarily, while skin closure of class III and IV wounds is associated with high rates of incisional SSIs (~25% to 50%). The superficial aspects of these latter types of wounds should be packed open and allowed to heal by secondary intention, although selective use of delayed primary closure has been associated with a reduction in incisional SSI rates.⁴⁹ It remains to be determined whether NNIS-type stratification schemes can be employed prospectively in order to target specific subgroups of patients which will benefit from the use of prophylactic antibiotic and/or specific wound management techniques. One clear example based on CoGeNT data from clinical trials is that class III wounds in healthy patients undergoing appendectomy for perforated or gangrenous appendicitis can be primarily closed as long as antibiotic therapy directed against aerobes and anaerobes is administered. This practice leads to SSI rates of approximately 3% to 4%.⁵⁰

Recent investigations have studied the effect of additional maneuvers in an attempt to further reduce the rate of SSIs. The adverse effects of hyperglycemia on WBC function have been well described.⁵¹ A number of recent studies in patients undergoing several different types of surgery describe increased risk of SSI in patients with hyperglycemia.^{52,53} Although randomized trials have not been performed, it is recommended that clinicians maintain appropriate blood sugar control in patients in the perioperative period to minimize the occurrence of SSI.

The respective effects of body temperature and the level of inhaled oxygen during surgery on SSI rates also have been studied, and both hypothermia and hypoxia during surgery are associated with a higher rate of SSIs. Although an initial study provided evidence that patients who received high levels of inhaled oxygen during colorectal surgery developed fewer SSIs,⁵⁴ a recent meta-analysis suggests that the overall benefit is small and may not warrant use.⁵⁵ Further evaluation via multicenter studies is needed prior to implementation of hyperoxia as standard therapy, but it is clear that intraoperative hypothermia and hypoxia should be prevented.

Effective therapy for incisional SSIs consists solely of incision and drainage without the additional use of antibiotics. Antibiotic therapy is reserved for patients in whom evidence of significant cellulitis is present, or who concurrently manifest a systemic inflammatory response syndrome. The open wound often is allowed to heal by secondary intention, with dressings being changed twice a day. The use of topical antibiotics and antiseptics to further wound healing remains unproven, although anecdotal studies indicate their potential utility in complex wounds that do not heal with routine measures.⁵⁶ Despite a paucity of prospective studies,⁵⁷ vacuum-assisted closure is increasingly used in management of large, complex open wounds and can be applied to wounds in locations that are difficult to manage with dressings (Fig. 6-2). One also should consider obtaining wound cultures in patients who develop SSIs and whom have been hospitalized or reside in long-term care facilities due to the increasing incidence of infection caused by multidrug resistant organisms. The treatment of organ/space infections is discussed in the following section.

Intra-Abdominal Infections

Microbial contamination of the peritoneal cavity is termed *peritonitis* or *intra-abdominal infection*, and is classified according to etiology. *Primary microbial peritonitis* occurs when microbes invade the normally sterile confines of the peritoneal cavity via hematogenous dissemination from a distant source of infection or



A



B

Figure 6-2. Negative pressure wound therapy in a patient after amputation for wet gangrene (A), and in a patient with enterocutaneous fistula (B). It is possible to adapt these dressings to fit difficult anatomy and provide appropriate wound care while reducing frequency of dressing change. It is important to evaluate the wound under these dressings if patient demonstrates signs of sepsis with an unidentified source, since typical clues of wound sepsis such as odor and drainage are hidden by the suction apparatus.

direct inoculation. This process is more common among patients who retain large amounts of peritoneal fluid due to ascites, and among those individuals who are being treated for renal failure via peritoneal dialysis. These infections invariably are monomicrobial and rarely require surgical intervention. The diagnosis is established based on identification of risk factors as noted previously, physical examination that reveals diffuse tenderness and guarding without localized findings, absence of pneumoperitoneum on an imaging study, the presence of more than 100 WBCs/mL, and microbes with a single morphology on Gram's stain performed on fluid obtained via paracentesis. Subsequent cultures typically will demonstrate the presence of gram positive organisms in patients undergoing peritoneal dialysis. In patients without this risk factor organisms can include *E. coli*, *K. pneumoniae*, pneumococci, and others, although many different pathogens can be causative. Treatment consists of administration of an antibiotic to which the organism is sensitive; often 14 to 21 days of therapy are required. Removal of indwelling devices (e.g., a peritoneal dialysis catheter or a peritoneovenous shunt) may be required for effective therapy of recurrent infections.

Secondary microbial peritonitis occurs subsequent to contamination of the peritoneal cavity due to perforation or severe inflammation and infection of an intra-abdominal organ. Examples include appendicitis, perforation of any portion of the gastrointestinal tract, or diverticulitis. As noted previously, effective therapy requires source control to resect or repair the diseased organ; débridement of necrotic, infected tissue and debris; and administration of antimicrobial agents directed against aerobes and anaerobes.⁵⁸ This type of antibiotic regimen should be chosen because in most patients the precise diagnosis cannot be established until exploratory laparotomy is performed, and the most morbid form of this disease process is colonic perforation, due to the large number of microbes present. A combination of agents or single agents with a broad spectrum of activity can be used for this purpose; conversion of a parenteral to an oral regimen when the patient's ileus resolves provides results similar to those achieved with intravenous antibiotics. Effective source control and antibiotic therapy is associated with low failure rates and a mortality rate of approximately 5% to 6%; inability to control the source of infection is associated with mortality greater than 40%.⁵⁹

The response rate to effective source control and use of appropriate antibiotics has remained approximately 70% to 90% over the past several decades.⁶⁰ Patients in whom standard therapy fails typically develop one or more of the following: an intra-abdominal abscess, leakage from a gastrointestinal anastomosis leading to postoperative peritonitis, or *tertiary (persistent) peritonitis*. The latter is a poorly understood entity that is more common in immunosuppressed patients in whom peritoneal host defenses do not effectively clear or sequester the initial secondary microbial peritoneal infection. Microbes such as *Enterococcus faecalis* and *faecium*, *Staphylococcus epidermidis*, *Candida albicans*, and *Pseudomonas aeruginosa* commonly are identified, typically in combination, and their presence may be due to their lack of responsiveness to the initial antibiotic regimen, coupled with diminished activity of host defenses. Unfortunately, even with effective antimicrobial agent therapy, this disease process is associated with mortality rates in excess of 50%.⁶¹

Formerly, the presence of an intra-abdominal abscess mandated surgical reexploration and drainage. Today, the vast

majority of such abscesses can be effectively diagnosed via abdominal computed tomographic (CT) imaging techniques and drained percutaneously. Surgical intervention is reserved for those individuals who harbor multiple abscesses, those with abscesses in proximity to vital structures such that percutaneous drainage would be hazardous, and those in whom an ongoing source of contamination (e.g., enteric leak) is identified. The necessity of antimicrobial agent therapy and precise guidelines that dictate duration of catheter drainage have not been established. A short course (3 to 7 days) of antibiotics that possess aerobic and anaerobic activity seems reasonable, and most practitioners leave the drainage catheter *in situ* until it is clear that cavity collapse has occurred, output is less than 10 to 20 mL/d, no evidence of an ongoing source of contamination is present, and the patient's clinical condition has improved.

Organ-Specific Infections

Hepatic abscesses are rare, currently accounting for approximately 15 per 100,000 hospital admissions in the United States. Pyogenic abscesses account for approximately 80% of cases, the remaining 20% being equally divided among parasitic and fungal forms.⁶² Formerly, pyogenic liver abscesses mainly were caused by pyelphlebitis due to neglected appendicitis or diverticulitis. Today, manipulation of the biliary tract to treat a variety of diseases has become a more common cause, although in nearly 50% of patients no cause is identified. The most common aerobic bacteria identified in recent series include *E. coli*, *K. pneumoniae*, and other enteric bacilli, enterococci, and *Pseudomonas* spp., while the most common anaerobic bacteria are *Bacteroides* spp., anaerobic streptococci, and *Fusobacterium* spp. *Candida albicans* and other related yeast cause the majority of fungal hepatic abscesses. Small (<1 cm), multiple abscesses should be sampled and treated with a 4 to 6 week course of antibiotics. Larger abscesses invariably are amenable to percutaneous drainage, with parameters for antibiotic therapy and drain removal similar to those mentioned previously. Splenic abscesses are extremely rare and are treated in a similar fashion. Recurrent hepatic or splenic abscesses may require operative intervention—unroofing and marsupialization or splenectomy, respectively.

Secondary pancreatic infections (e.g., infected pancreatic necrosis or pancreatic abscess) occur in approximately 10% to 15% of patients who develop severe pancreatitis with necrosis. The surgical treatment of this disorder was pioneered by Bradley and Allen, who noted significant improvements in outcome for patients undergoing repeated pancreatic débridement of infected pancreatic necrosis.⁶³ Current care of patients with severe acute pancreatitis includes staging with dynamic, contrast material-enhanced helical CT scan to evaluate the extent of pancreatitis (unless significant renal dysfunction exists in which case one should forego the use of contrast material) coupled with the use of one of several prognostic scoring systems. Patients who exhibit clinical signs of instability (e.g., oliguria, hypoxemia, large-volume fluid resuscitation) should be carefully monitored in the ICU and undergo follow-up contrast enhanced CT examination when renal function has stabilized to evaluate for development of local pancreatic complications (Fig. 6-3). A recent change in practice has been the elimination of the routine use of prophylactic antibiotics for prevention of infected pancreatic necrosis. Enteral feedings initiated early, using nasojejunal feeding tubes placed past the ligament of Treitz, have been associated with decreased development of infected pancreatic



Figure 6-3. Contrast-enhanced CT scan of pancreas 1½ weeks after presentation showing large central peripancreatic fluid collection.

necrosis, possibly due to a decrease in gut translocation of bacteria. These topics have been recently reviewed.^{64,65}

The presence of secondary pancreatic infection should be suspected in patients whose systemic inflammatory response (fever, elevated WBC count, or organ dysfunction) fails to resolve, or in those individuals who initially recuperate, only to develop sepsis syndrome 2 to 3 weeks later. CT-guided aspiration of fluid from the pancreatic bed for performance of Gram's stain and culture analysis can be useful. A positive Gram's stain or culture from CT-guided aspiration, or identification of gas within the pancreas on CT scan, mandate surgical intervention.

The approach of open necrosectomy with repeated debridements, although life saving, is associated with significant morbidity and prolonged hospitalization. Efforts to reduce the amount of surgical injury, while still preserving the improved outcomes associated with debridement of the infected sequestrum have led to a variety of less invasive approaches.⁶⁶ These include endoscopic approaches, laparoscopic approaches and other minimally invasive approaches. There are a limited number of randomized trials reporting the use of these new techniques currently. An important concept common to all of these approaches, however, is the attempt to delay surgical intervention, since a number of trials have identified increased mortality when intervention occurs during the first two weeks of illness.

Data supporting the use of endoscopic approaches to this problem include nearly a dozen case series and a randomized trial.^{67,68} The reported mortality rate was 5%, with a 30% complication rate. Most authors noted the common requirement for multiple endoscopic debridements (similar to the open approach), with a median of 4 endoscopic sessions required. Fewer series report experience with the laparoscopic approach, either transgastric or transperitoneal, entering the necrosis through the transverse mesocolon or gastrocolic ligament. The laparoscopic technique is carefully described in a recent publication.⁶⁹ Laparoscopic intervention is limited by the difficulty in achieving multiple debridements and the technical expertise required to achieve an adequate debridement. Mortality in 65 patients in 9 case series reported was 6% overall.

Debridement of necrosis through a lumbar approach has been advocated by a number of authors. This approach, developed with experience in a large number of patients,⁷⁰ has been recently subjected to a single center randomized prospective

trial.⁷¹ This approach includes delay of intervention when possible until 4 weeks after the onset of disease. Patients receive transgastric or preferably retroperitoneal drainage of the sequestrum. If patients do not improve over 72 hours, they are treated with video-assisted retroperitoneal drainage (VARD), consisting of dilation of the retroperitoneal drain tract, placement of and irrigation, and debridement of the pancreatic bed (Fig. 6-4).

Repeat debridements are performed as clinically indicated, with most patients requiring multiple debridements. In the trial reported, patients randomized to VARD ($n=43$) compared to those randomized to the standard open necrosectomy ($n=45$) had a decreased incidence of the composite endpoint of complications and death (40% vs. 69%), with comparable mortality rate, hospital, and ICU lengths of stay. Patients randomized to VARD had fewer incisional hernias, new-onset diabetes, and need for pancreatic enzyme supplementation.

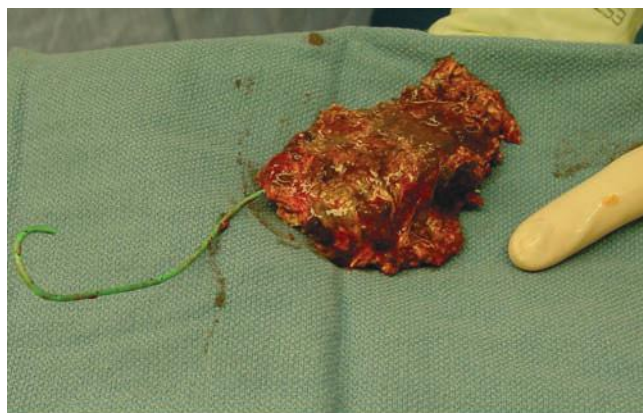
It is apparent that patients with infected pancreatic necrosis can safely undergo procedures that are more minimal than the gold-standard open necrosectomy with good outcomes. However, to obtain good outcomes these approaches require an experienced multidisciplinary team consisting of interventional radiologists, gastroenterologists, surgeons, and others. Important concepts for successful management include careful pre-operative planning, delay (if possible) to allow maturation of the fluid collection, and the willingness to repeat procedures as necessary till the majority if not all nonviable tissue has been removed.

Infections of the Skin and Soft Tissue

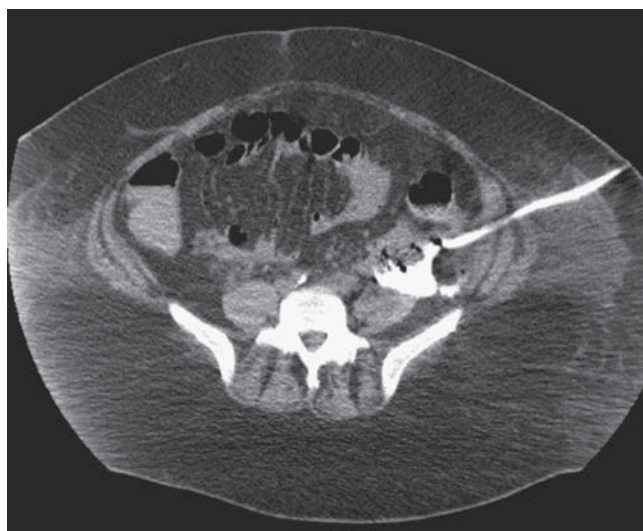
These infections can be classified according to whether or not surgical intervention is required. For example, superficial skin and skin structure infections such as cellulitis, erysipelas, and lymphangitis invariably are effectively treated with antibiotics alone, although a search for a local underlying source of infection should be undertaken. Generally, drugs that possess activity against the causative gram-positive skin microflora are selected. Furuncles or boils may drain spontaneously or require surgical incision and drainage. Antibiotics are prescribed if significant cellulitis is present or if cellulitis does not rapidly resolve after surgical drainage. Community-acquired methicillin resistant *Staphylococcus aureus* (MRSA) infection should be suspected if infection persists after treatment with adequate drainage and administration of first line antibiotics. These infections may require more aggressive drainage and altered antimicrobial therapy.⁷²

Aggressive soft tissue infections are rare, difficult to diagnose, and require immediate surgical intervention plus administration of antimicrobial agents. Failure to do so results in an extremely high mortality rate (~80%–100%), and even with rapid recognition and intervention, current mortality rates are high (16%–24%).⁷³ Eponyms and classification in the past have been a hodgepodge of terminology, such as Meleney's synergist gangrene, rapidly spreading cellulitis, gas gangrene, and necrotizing fasciitis, among others. Today it seems best to delineate these serious infections based on the soft tissue layer(s) of involvement (e.g., skin and superficial soft tissue, deep soft tissue, and muscle) and the pathogen(s) that cause them.

Patients at risk for these types of infections include those who are elderly, immunosuppressed, or diabetic; those who suffer from peripheral vascular disease; or those with a combination of these factors. The common thread among these host factors appears to be compromise of the fascial blood supply to some degree, and if this is coupled with the introduction of



A



B



C

Figure 6-4. Infected pancreatic necrosis. (A) Open necrosectomy specimen with pancreatic stent in situ. It is important to gently debride only necrotic pancreatic tissue, relying on repeated operation to ensure complete removal. (B) For video-assisted retroperitoneal debridement (VARD), retroperitoneal access is gained through radiologic placement of a drain, followed by dilation 2-3 days later. (C) Retroperitoneal cavity seen through endoscope during VARD.

exogenous microbes, the result can be devastating. However, it is of note that over the last decade, extremely aggressive necrotizing soft tissue infections among healthy individuals due to streptococci have been described as well.

Initially, the diagnosis is established solely upon a constellation of clinical findings, not all of which are present in every patient. Not surprisingly, patients often develop sepsis syndrome or septic shock without an obvious cause. The extremities, perineum, trunk, and torso are most commonly affected, in that order. Careful examination should be undertaken for an entry site such as a small break or sinus in the skin from which grayish, turbid semipurulent material (“dishwater pus”) can be expressed, as well as for the presence of skin changes (bronze hue or brawny induration), blebs, or crepitus. The patient often develops pain at the site of infection that appears to be out of proportion to any of the physical manifestations. Any of these findings mandates immediate surgical intervention, which should consist of exposure and direct visualization of potentially infected tissue (including deep soft tissue, fascia, and underlying muscle) and radical resection of affected areas. Radiologic studies should not be undertaken in patients in whom the diagnosis seriously is considered, as they delay surgical intervention and frequently provide confusing information. Unfortunately, surgical extirpation of infected tissue frequently entails amputation and/or disfiguring procedures; however, incomplete procedures are associated with higher rates of morbidity and mortality (Fig. 6-5).

During the procedure a Gram’s stain should be performed on tissue fluid. Antimicrobial agents directed against Gram-positive and Gram-negative aerobes and anaerobes (e.g., vancomycin plus a carbapenem), as well as high-dose aqueous penicillin G (16,000,000 to 20,000,000 U/d), the latter to treat clostridial pathogens, should be administered. Approximately 50% of such infections are polymicrobial, the remainder being caused by a single organism such as *Streptococcus pyogenes*, *Pseudomonas aeruginosa*, or *Clostridium perfringens*. The microbiology of these polymicrobial infections is similar to that of secondary microbial peritonitis, with the exception that Gram-positive cocci are more commonly encountered. Most patients should be returned to the operating room on a scheduled basis to determine if disease progression has occurred. If so, additional resection of infected tissue and debridement should take place. Antibiotic therapy can be refined based on culture and sensitivity results, particularly in the case of monomicrobial soft tissue infections. Hyperbaric oxygen therapy may be of use in patients with infection caused by gas-forming organisms (e.g., *Clostridium perfringens*), although the evidence to support efficacy is limited to underpowered studies and case reports. In the absence of such infection, hyperbaric oxygen therapy has not shown to be effective.⁷⁴

Postoperative Nosocomial Infections

Surgical patients are prone to develop a wide variety of nosocomial infections during the postoperative period, which include SSIs, UTIs, pneumonia, and bacteremia. SSIs are discussed earlier, and the latter types of nosocomial infections are related to prolonged use of indwelling tubes and catheters for the purpose of urinary drainage, ventilation, and venous and arterial access, respectively.

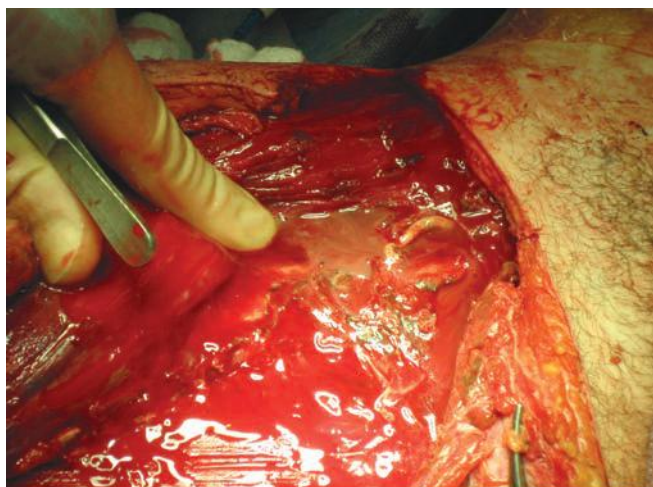
The presence of a postoperative UTI should be considered based on urinalysis demonstrating WBCs or bacteria, a positive test for leukocyte esterase, or a combination of these elements. The diagnosis is established after $>10^4$ CFU/mL of microbes are identified by culture techniques in symptomatic patients,



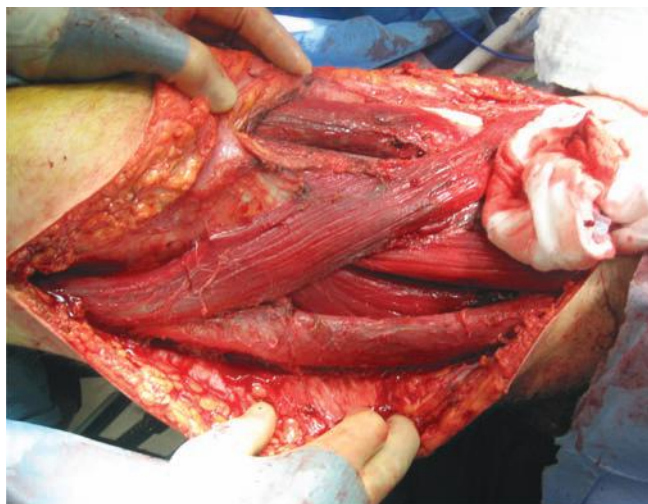
A



B



C



D

Figure 6-5 Necrotizing soft tissue infection. (A) This patient presented with hypotension due to severe late necrotizing fasciitis and myositis due to beta-hemolytic streptococcal infection. The patient succumbed to his disease after 16 hours despite aggressive debridement. (B) This patient presented with spreading cellulites and pain on motion of his right hip 2 weeks after total colectomy. Cellulitis on right anterior thigh is outlined. (C) Classic dishwater edema of tissues with necrotic fascia. (D) Right lower extremity after debridement of fascia to viable muscle.

or $>10^5$ CFU/mL in asymptomatic individuals. Treatment for 3 to 5 days with a single antibiotic directed against the most common organisms (e.g., *E. Coli*, *K. pneumonia*) that achieves high levels in the urine is appropriate. Initial therapy is directed by Gram's stain results and is refined as culture results become available. Postoperative surgical patients should have indwelling urinary catheters removed as quickly as possible, typically within 1 to 2 days, as long as they are mobile, to avoid the development of a UTI.

Prolonged mechanical ventilation is associated with nosocomial pneumonia. These patients present with more severe disease, are more likely to be infected with drug-resistant pathogens, and suffer increased mortality compared to patients who develop community-acquired pneumonia. The diagnosis of pneumonia is established by presence of a purulent sputum, elevated leukocyte count, fever, and new chest X-ray abnormalities, such as consolidation. The presence of two of the clinical findings, plus chest X-ray findings, significantly increases

the likelihood of pneumonia.⁷⁵ Consideration should be given to performing bronchoalveolar lavage to obtain samples for Gram's stain and culture. Some authors advocate quantitative cultures as a means to identify a threshold for diagnosis.⁷⁶ Surgical patients should be weaned from mechanical ventilation as soon as feasible, based on oxygenation and inspiratory effort, as prolonged mechanical ventilation increases the risk of nosocomial pneumonia.

Infection associated with indwelling intravascular catheters has become a common problem among hospitalized patients. Because of the complexity of many surgical procedures, these devices are increasingly used for physiologic monitoring, vascular access, drug delivery, and hyperalimentation. Among the several million catheters inserted each year in the United States, approximately 25% will become colonized, and approximately 5% will be associated with bacteremia. Duration of catheterization, insertion or manipulation under emergency or nonsterile conditions, use for hyperalimentation, and the use of multilumen catheters increase the risk of infection. Use of a central line insertion protocol that includes full barrier precautions and chlorhexidine skin prep has been shown to decrease the incidence of infection.⁷⁷ Although no randomized trials have been performed, peripherally inserted central venous catheters have a catheter-related infection rate similar to those inserted in the subclavian or jugular veins.⁷⁸

Many patients who develop intravascular catheter infections are asymptomatic, often exhibiting solely an elevation in the blood WBC count. Blood cultures obtained from a peripheral site and drawn through the catheter that reveal the presence of the same organism increase the index of suspicion for the presence of a catheter infection. Obvious purulence at the exit site of the skin tunnel, severe sepsis syndrome due to any type of organism when other potential causes have been excluded, or bacteremia due to Gram-negative aerobes or fungi should lead to catheter removal. Selected catheter infections due to low-virulence microbes such as *Staphylococcus epidermidis* can be effectively treated in approximately 50% to 60% of patients with a 14- to 21-day course of an antibiotic, which should be considered when no other vascular access site exists.⁷⁹ The use of antibiotic-bonded catheters and chlorhexidine sponges at the insertion site have been associated with lower rates of colonization.⁷⁷ Use of ethanol or antimicrobial catheter "locks" have shown promise in reducing incidence of infection in dialysis catheters.⁸⁰ The surgeon should carefully consider the need for any type of vascular access device, rigorously attend to their maintenance to prevent infection, and remove them as quickly as possible. Use of systemic antibacterial or antifungal agents to prevent catheter infection is of no utility and is contraindicated.

Sepsis

Severe sepsis is increasing in incidence, with over 1.1 million cases estimated per year in the United States with an annual cost of 24 billion dollars. This rate is expected to increase as the population of aged in the United States increases. One third of sepsis cases occur in surgical populations and sepsis is a major cause of morbidity and mortality.⁸¹ The treatment of sepsis has improved dramatically over the last decade, with mortality rates dropping to under 30%. Factors contributing to this improvement in mortality relate both to recent randomized prospective trials demonstrating improved outcomes with new therapies, and to improvements in the process of care delivery to the sepsis patient. The "Surviving Sepsis Campaign," a multidisciplinary

group that worked to develop treatment recommendations has published guidelines incorporating evidence-based treatment strategies most recently in 2013.¹³ These guidelines are summarized in Table 6-9.

Patients presenting with severe sepsis should receive resuscitation fluids to achieve a central venous pressure target of 8-12 mm Hg, with a goal of mean arterial pressure of ≥ 65 mmHg and urine output of ≥ 0.5 mL/kg/h. Delaying this resuscitative step for as little as 3 hours until arrival in the ICU has been shown to result in poor outcome.⁸² Typically this goal necessitates early placement of central venous catheter.

A number of studies have demonstrated the importance of early empirical antibiotic therapy in patients who develop sepsis or nosocomial infection. This therapy should be initiated as soon as possible with broad spectrum antibiotics directed against most likely organisms, since early appropriate antibiotic therapy has been associated with significant reductions in mortality, and delays in appropriate antibiotic administration are associated with increased mortality. Use of institutional and unit specific sensitivity patterns are critical in selecting an appropriate agent for patients with nosocomial infection. It is key, however, to obtain cultures of appropriate areas without delaying initiating antibiotics so that appropriate adjustment of antibiotic therapy can take place when culture results return.

Additionally, early identification and treatment of septic sources is key for improved outcomes in patients with sepsis. Although there are no randomized trials demonstrating this concept, repeated evidence in studies of patients who develop intraabdominal infection, necrotizing soft tissue infection, and other types of infections demonstrate increased mortality with delayed treatment. As discussed earlier, one exception is that of infected pancreatic necrosis.

Multiple recent trials have evaluated the use of vasopressors and inotropes for treatment of septic shock. The current first-line agent for treatment of hypotension is norepinephrine. It is important to titrate therapy based on other parameters such as mixed venous oxygen saturation and plasma lactate levels as well as mean arterial pressure to reduce the risk of vasopressor-induced perfusion deficits. Several recent randomized trials have failed to demonstrate benefit with use of pulmonary arterial catheterization, leading to a significant decrease in its use.

A number of other adjunctive therapies are useful in treatment of the patient with severe sepsis and septic shock. Low-dose corticosteroids (hydrocortisone at ≤ 300 mg/day) can be used in patients with septic shock who are not responsive to fluids and vasopressors. However, a recent randomized trial failed to show survival benefit. Patients with acute lung injury associated with sepsis should receive mechanical ventilation with tidal volumes of 6 mL/kg and pulmonary airway plateau pressures of ≤ 30 cm H₂O. Finally, red blood cell transfusion should be reserved for patients with hemoglobin of <7 grams/dL, with a more liberal transfusion strategy reserved for those patients with severe coronary artery disease, ongoing blood loss, or severe hypoxemia.

Resistant Organisms: In the 1940s, penicillin was first produced for widespread clinical use. Within a year of its introduction, the first resistant strains of *Staphylococcus aureus* were identified. There are two major components that are responsible for antibiotic resistance. First, there may be a genetic component innate to the organism that prevents an effect of a particular antibiotic. For instance, if an organism does not have a target receptor specific to the mechanism of action of a particular antibiotic,

Table 6-9

Summary of Surviving Sepsis Campaign guidelines**Initial Evaluation and Infection Issues**

Initial resuscitation: Begin resuscitation immediately in patients with hypotension or elevated serum lactate with resuscitation goal of central venous pressure (CVP) 8 to 12 mm Hg, mean arterial pressure of ≥ 65 mm Hg, urine output of ≥ 0.5 mL/kg/h, and mixed venous oxygen saturation of 65%.

Target resuscitation to normalize lactate in patients with elevated lactate levels.

Diagnosis: Obtain appropriate cultures prior to antibiotics but do not delay antibiotic therapy. Use rapid antigen assays in patients with suspected fungal infection. Imaging studies should be performed promptly to confirm a source of infection.

Antibiotic therapy: Begin IV antibiotic therapy as early as possible: should be within the first hour after recognition of severe sepsis/septic shock. Use broad spectrum antibiotic regimen with penetration into presumed source, reassess regimen daily with deescalation as appropriate. Discontinue antibiotics in 7–10 d for most infections, stop antibiotics for noninfectious issues.

Source control: Establish anatomic site of infection as rapidly as possible, implement source control measures immediately after initial resuscitation. Remove intravascular access devices if potentially infected.

Infection prevention: Selective oral and digestive tract decontamination.

Hemodynamic Support and Adjunctive Therapy

Fluid therapy: Fluid resuscitate using crystalloid, using fluid volumes of 1000 mL (crystalloid), target CVP of 8 to 12 mm Hg.

Vasopressors/Inotropic Therapy: Maintain MAP of ≥ 65 mm Hg, centrally-administered norepinephrine is first-line choice. Dopamine should not be used for “renal protection,” insert arterial catheters for patients requiring vasopressors. Phenylephrine is not recommended in treatment of septic shock. Dobutamine infusion can be used in setting of myocardial dysfunction. Do not use strategy of targeting supranormal cardiac index.

Steroids: Consider intravenous hydrocortisone (dose ≤ 300 mg/d) for adult septic shock when hypotension responds poorly to fluids and vasopressors.

Other Supportive Therapy

Blood product administration: Transfuse red blood cells when hemoglobin decreases to < 7.0 g/dL.

Mechanical ventilation: Target an initial tidal volume of 6 mL/kg body weight and plateau pressure of ≤ 30 cm H₂O in patients with acute lung injury. Use positive end-expiratory pressure to avoid lung collapse. Use a weaning protocol to evaluate the potential for discontinuing mechanical ventilation. Pulmonary artery catheter is not indicated for routine monitoring.

Sedation: Minimize sedation using specific titration endpoints.

Glucose control: Use protocolized approach to blood glucose management targeting upper blood glucose target of 180 mg/dL.

Prophylaxis: Use stress ulcer (proton pump inhibitor or H₂ blocker) and deep venous thrombosis (low-dose unfractionated or fractionated heparin) prophylaxis.

Limitation of support: Discuss advance care planning with patients and families and set realistic expectations.

Adapted from Dellinger et. al¹³

the antibiotic will not be effective against this organism. A good example is penicillin and Gram-negative organisms, as these microbes lack penicillin-binding proteins. The second component driving resistance is that related to antibiotic selection. Over generations of exposure to a particular antibiotic, selection pressure will drive proliferation of more organisms resistant to that antibiotic. It is this mechanism that leads to antibiotic resistance in the world today, given that there are millions of kilograms of antibiotics used annually in people, in agriculture, and for animal use. This has led to antibiotic resistance described in all classes of antibiotics in common use today. Antibiotic resistance comes at a high cost, with a significant increase in mortality associated with infection from resistant organisms, and an economic cost of billions of dollars per year.

Resistance mechanisms are varied, and include one of three routes. Resistance can be intrinsic to the organism (natural resistance), can be mutational and mediated by changes in the chromosomal makeup of the organism, and finally can be mediated by extrachromosomal transfer of genetic material via

transposons or plasmids. Resistance due to mutation includes mechanisms mediated by target site modification, reduced permeability/uptake, metabolic bypass, or derepression of multi-drug efflux systems. Genes transferred via plasmid or transposon include those that cause drug inactivation, increases in antibiotic efflux systems, target site modification, and metabolic bypass.

There are several drug resistant organisms of interest to the surgeon. MRSA occurs as a hospital-associated infection more common in chronically ill patients receiving multiple courses of antibiotics. However, recent strains of MRSA have emerged in the community among patients without preexisting risk factors for disease.⁷² These strains, which produce a toxin known as *Panton-Valentin leukocidin*, make up an increasingly high percentage of surgical site infections since they are resistant to commonly employed prophylactic antimicrobial agents.⁸³ Extended spectrum β -lactamase (ESBL)-producing strains of *Enterobacteriaceae*, originally geographically localized and infrequent, have become much more widespread and common in the last decade.⁸⁴ These strains, typically *Klebsiella* or *E coli*

species, produce a plasmid-mediated inducible β -lactamase. Commonly encountered plasmids also confer resistance to many other antibiotic classes (multidrug resistance). A common laboratory finding with ESBL is sensitivity to first-, second-, or third- generation cephalosporins with resistance to others. Unfortunately, use of this seemingly active agent leads to rapid induction of resistance and failure of antibiotic therapy. The appropriate antibiotic choice in this setting is a carbapenem. While *Enterococcus* used to be considered a low virulence organism in the past, infections caused by *E. faecium* and *faecalis* have been found to be increasingly virulent, especially in the immunocompromised host. The last decade has seen increased isolation of a vancomycin-resistant strain of *Enterococcus*.⁸⁵ This resistance is transposon-mediated via the *vanA* gene and is typically seen in *E. faecium* strains. A real concern in this setting is transfer of genetic material to *S. aureus* in a host coinfecting with both organisms. This is thought to be the mechanism behind the half dozen recently described cases of vancomycin resistance in *S. aureus*.

Blood-Borne Pathogens

While alarming to contemplate, the risk of human immunodeficiency virus (HIV) transmission from patient to surgeon is low. As of May 2011, there had been six cases of surgeons with HIV seroconversion from a possible occupational exposure, with no new cases reported since 1999. Of the numbers of health care workers with likely occupationally acquired HIV infection ($n = 200$), surgeons were one of the lower risk groups (compared to nurses at 60 cases and nonsurgeon physicians at 19 cases).⁸⁶ The estimated risk of transmission from a needlestick from a source with HIV-infected blood is estimated at 0.3%. Transmission of HIV (and other infections spread by blood and body fluid) from patient to health care worker can be minimized by observation of universal precautions, which include the following: (a) routine use of barriers (such as gloves and/or goggles) when anticipating contact with blood or body fluids, (b) washing of hands and other skin surfaces immediately after contact with blood or body fluids, and (c) careful handling and disposal of sharp instruments during and after use.

7► Postexposure prophylaxis for HIV has significantly decreased the risk of seroconversion for health care workers with occupational exposure to HIV. Steps to initiate postexposure prophylaxis should be initiated within hours rather than days for the most effective preventive therapy. Postexposure prophylaxis with a two- or three-drug regimen should be initiated for health care workers with significant exposure to patients with an HIV-positive status. If a patient's HIV status is unknown, it may be advisable to begin postexposure prophylaxis while testing is carried out, particularly if the patient is at high risk for infection due to HIV (e.g., intravenous narcotic use). Generally, postexposure prophylaxis is not warranted for exposure to sources with unknown status, such as deceased persons or needles from a sharps container.

The risks for surgeons of acquiring HIV infection have recently been evaluated by Goldberg and coauthors.⁸⁷ They noted that the risks are related to the prevalence of HIV infection in the population being cared for, the probability of transmission from a percutaneous injury suffered while caring for an infected patient, the number of such injuries sustained, and the use of postexposure prophylaxis. Annual calculated risks in Glasgow, Scotland, ranged from one in 200,000 for general surgeons not utilizing postexposure prophylaxis to as low as

one in 10,000,000 with use of routine postexposure prophylaxis after significant exposures.

Hepatitis B virus (HBV) is a DNA virus that affects only humans. Primary infection with HBV generally is self-limited, but can cause fulminant hepatitis or progress to a chronic carrier state. Death from chronic liver disease or hepatocellular cancer occurs in roughly 30% of chronically infected persons. Surgeons and other health care workers are at high risk for this blood-borne infection and should receive the HBV vaccine; children are routinely vaccinated in the United States.⁸⁸ This vaccine has contributed to a significant decline in the number of new cases of HBV per year in the United States, from approximately 250,000 annually in the 1980s to 3,350 in 2010.^{89,90} This is truly one of the unsung victories in vaccination strategy in the last 20 years.

Hepatitis C virus (HCV), previously known as non-A, non-B hepatitis, is a RNA flavivirus first identified specifically in the late 1980s. This virus is confined to humans and chimpanzees. A chronic carrier state develops in 75% to 80% of patients with the infection, with chronic liver disease occurring in three-fourths of patients who develop chronic infection. The number of new infections per year has declined since the 1980s due to routine testing of blood donors for this virus. Fortunately, HCV is not transmitted efficiently through occupational exposures to blood, with the seroconversion rate after accidental needlestick approximately 1.8%.⁹¹ To date, a vaccine to prevent HCV infection has not been developed. Experimental studies in chimpanzees with HCV immunoglobulin using a model of needlestick injury have failed to demonstrate a protective effect, and no effective antiviral agents for postexposure prophylaxis are available. Treatment of patients who develop HCV infection includes ribavirin and pegylated gamma interferon.⁹²

BIOLOGIC WARFARE AGENTS

Several infectious organisms have been studied by the United States and the former Soviet Union and presumably other entities for potential use as biologic weapons. Programs involving biologic agents in the United States were halted by presidential decree in 1971. However, concern remains that these agents could be used by rogue states or terrorist organizations as weapons of mass destruction, as they are relatively inexpensive to make in terms of infrastructure development. A related issue is the recent controversy regarding publication of genetic sequences and synthesis of virulent viruses, such as the 1918 influenza strain, responsible for death of an estimated 3% of the world population. Given these concerns, physicians, including surgeons should familiarize themselves with the manifestations of infection due to these pathogens. The typical agent is selected for the ability to be spread via the inhalational route, as this is the most efficient mode of mass exposure. Several potential agents are discussed in the following sections.

Bacillus anthracis (Anthrax)

Anthrax is a zoonotic disease occurring in domesticated and wild herbivores. The first identification of inhalational anthrax as a disease occurred among woolsorters in England in the late 1800s. The largest recent epidemic of inhalational anthrax occurred in Sverdlovsk, Russia, in 1979 after accidental release of anthrax spores from a military facility. Inhalational anthrax develops after a 1- to 6-day incubation period, with

nonspecific symptoms, including malaise, myalgia, and fever. Over a short period of time, these symptoms worsen, with development of respiratory distress, chest pain, and diaphoresis. Characteristic chest roentgenographic findings include a widened mediastinum and pleural effusions. A key aspect in establishing the diagnosis is eliciting an exposure history. Rapid antigen tests are currently under development for identification of this gram-positive rod. Postexposure prophylaxis consists of administration of either ciprofloxacin or doxycycline.⁹³ If an isolate is demonstrated to be penicillin-sensitive, the patient should be switched to amoxicillin. Inhalational exposure followed by the development of symptoms is associated with a high mortality rate. Treatment options include combination therapy with ciprofloxacin, clindamycin, and rifampin; clindamycin added to block production of toxin, while rifampin penetrates into the central nervous system and intracellular locations.

***Yersinia pestis* (Plague)**

Plague is caused by the Gram-negative organism *Yersinia pestis*. The naturally occurring disease in humans is transmitted via flea bites from rodents. It was the first biologic warfare agent, and was used in the Crimean city of Caffa by the Tartar army, whose soldiers catapulted bodies of plague victims at the Genoese. When plague is used as a biologic warfare agent, clinical manifestations include epidemic pneumonia with blood-tinged sputum if aerosolized bacteria are used, or bubonic plague if fleas are used as carriers. Individuals who develop a painful enlarged lymph node lesion termed a “bubo” associated with fever, severe malaise, and exposure to fleas should be suspected to have plague. Diagnosis is confirmed via aspirate of the bubo and a direct antibody stain to detect plague bacillus. Typical morphology for this organism is that of a bipolar safety-pin-shaped Gram-negative organism. Postexposure prophylaxis for patients exposed to plague consists of doxycycline. Treatment of the pneumonic or bubonic/septicemic form includes administration of either streptomycin, an aminoglycoside, doxycycline, ciprofloxacin, levofloxacin, or chloramphenicol.⁹⁴

Smallpox

Variola, the causative agent of smallpox, was a major cause of infectious morbidity and mortality until its eradication in the late 1970s. During the European colonization of North America, British commanders may have used it against native inhabitants and the colonists by distribution of blankets from smallpox victims. Even in the absence of laboratory-preserved virus, the prolonged viability of variola virus has been demonstrated in scabs up to 13 years after collection; the potential for reverse genetic engineering using the known sequence of smallpox also makes it a potential biologic weapon. This has resulted in the United States undertaking a vaccination program for key health care workers.⁹⁵ Variola virus is highly infectious in the aerosolized form; after an incubation period of 10 to 12 days, clinical manifestations of malaise, fever, vomiting, and headache appear, followed by development of a characteristic centripetal rash (which is found to predominate on the face and extremities). The fatality rate may reach 30%. Postexposure prophylaxis with smallpox vaccine has been noted to be effective for up to 4 days postexposure. Cidofovir, an acyclic nucleoside phosphonate analogue, has demonstrated activity in animal models of poxvirus infections and may offer promise for the treatment of smallpox.⁹⁶

***Francisella tularensis* (Tularemia)**

The principal reservoir of this Gram-negative aerobic organism is the tick. After inoculation, this organism proliferates within macrophages. This organism has been considered a potential bioterrorist threat due to a very high infectivity rate after aerosolization. Patients with tularemia pneumonia develop a cough and demonstrate pneumonia on chest roentgenogram. Enlarged lymph nodes occur in approximately 85% of patients. The organism can be cultured from tissue samples, but this is difficult, and the diagnosis is based on acute-phase agglutination tests. Treatment of inhalational tularemia consists of administration of an aminoglycoside or second-line agents such as doxycycline and ciprofloxacin.

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7 chapter

Trauma

Clay Cothren Burlew and Ernest E. Moore

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INTRODUCTION

Trauma, or injury, is defined as cellular disruption caused by an exchange with environmental energy that is beyond the body's resilience which is compounded by cell death due to ischemia/reperfusion. Trauma remains the most common cause of death for all individuals between the ages of 1 and 44 years

and is the third most common cause of death regardless of age.¹ It is also the leading cause of years of productive life lost. Unintentional injuries account for over 110,000 deaths per year, with motor vehicle collisions accounting for over 40%. Homicides, suicides, and other causes are responsible for another 50,000 deaths each year. However, death rate underestimates the magnitude of the societal toll. For example, in 2004 there were approximately 167,000 injury-related deaths, but 29.6 million injured patients treated in emergency departments (EDs). Injury-related medical expenditures are estimated to be \$117 billion each year in the United States.² The aggregate lifetime cost for all injured patients is estimated to be in excess of \$260 trillion. For these reasons, trauma must be considered a major public health issue. The American College of Surgeons Committee on Trauma addresses this issue by assisting in the development of trauma centers and systems. The organization of trauma systems has had a significant favorable impact on patient outcomes.³⁻⁵

INITIAL EVALUATION AND RESUSCITATION OF THE INJURED PATIENT

Primary Survey

The Advanced Trauma Life Support (ATLS) course of the American College of Surgeons Committee on Trauma was developed in the late 1970s, based on the premise that appropriate and timely care can significantly improve the outcome for the injured patient.⁶ ATLS provides a structured approach to

the trauma patient with standard algorithms of care; it emphasizes the “golden hour” concept that timely, prioritized interventions are necessary to prevent death and disability. The ATLS format and basic tenets are followed throughout this chapter, with some modifications. The initial management of seriously injured patients consists of phases that include the primary survey/concurrent resuscitation, the secondary survey/diagnostic evaluation, definitive care, and the tertiary survey. The first step in patient management is performing the primary survey, the goal of which is to identify and treat conditions that constitute an immediate threat to life. The ATLS course refers to the primary survey as assessment of the “ABCs” (Airway with cervical spine protection, Breathing, and Circulation). Although the concepts within the primary survey are presented in a sequential fashion, in reality they are pursued simultaneously in coordinated team resuscitation. Life-threatening injuries must be identified (Table 7-1) and treated before being distracted by the secondary survey.

Airway Management with Cervical Spine Protection Ensuring a patent airway is the first priority in the primary survey. This is essential, because efforts to restore cardiovascular integrity will be futile unless the oxygen content of the blood is adequate. Simultaneously, all patients with blunt trauma require cervical spine immobilization until injury is excluded. This is typically accomplished by applying a hard collar or placing sandbags on both sides of the head with the patient's forehead taped across the bags to the backboard. Soft collars do not effectively immobilize the cervical spine. For penetrating neck wounds, however, cervical collars are not believed useful because they provide no benefit, but may interfere with assessment and treatment.^{7,8}

In general, patients who are conscious, without tachypnea, and have a normal voice are unlikely to require early airway intervention. Exceptions are penetrating injuries to the neck with an expanding hematoma; evidence of chemical or thermal

Key Points

- 1▶ Trauma remains the most common cause of death for all individuals between the ages of 1 and 44 years and is the third most common cause of death regardless of age.
- 2▶ The initial management of seriously injured patients consists of performing the primary survey (the “ABCs”—Airway with cervical spine protection, Breathing, and Circulation); the goals of the primary survey are to identify and treat conditions that constitute an immediate threat to life.
- 3▶ All patients with blunt injury should be assumed to have unstable cervical spine injuries until proven otherwise; one must maintain cervical spine precautions and in-line stabilization.
- 4▶ Patients with ongoing hemodynamic instability, whether “nonresponders” or “transient responders,” require prompt intervention; one must consider the four categories of shock that may represent the underlying pathophysiology: hemorrhagic, cardiogenic, neurogenic, and septic.
- 5▶ Indications for immediate operative intervention for penetrating cervical injury include hemodynamic instability and significant external arterial hemorrhage; the management algorithm for hemodynamically stable patients is based on the presenting symptoms and anatomic location of injury, with the neck being divided into three distinct zones.
- 6▶ The gold standard for determining if there is a blunt descending torn aorta injury is CT scanning; indications are primarily based on injury mechanisms.
- 7▶ The abdomen is a diagnostic black box. However, physical examination and ultrasound can rapidly identify patients requiring emergent laparotomy. Computed tomographic (CT) scanning is the mainstay of evaluation in the remaining patients to more precisely identify the site and magnitude of injury.
- 8▶ Manifestation of the “bloody vicious cycle” (the lethal combination of coagulopathy, hypothermia, and metabolic acidosis) is the most common indication for damage control surgery. The primary objectives of damage control laparotomy are to control bleeding and limit GI spillage.
- 9▶ Blunt injuries to the carotid and vertebral arteries are usually managed with systemic antithrombotic therapy.
- 10▶ The abdominal compartment syndrome may be primary (i.e., due to the injury of abdominal organs, bleeding, and packing) or secondary (i.e., due to reperfusion visceral edema, retroperitoneal edema, and ascites).

injury to the mouth, nares, or hypopharynx; extensive subcutaneous air in the neck; complex maxillofacial trauma; or airway bleeding. Although these patients may initially have an adequate airway, it may become obstructed if soft tissue swelling, hematoma formation, or edema progresses. In these cases, pre-emptive intubation should be performed before airway access becomes challenging.

Table 7-1

Immediately life-threatening injuries to be identified during the primary survey

Airway

- Airway obstruction
- Airway injury

Breathing

- Tension pneumothorax
- Open pneumothorax
- Massive air leak
- Flail chest with underlying pulmonary contusion

Circulation

- Hemorrhagic shock
 - Massive hemothorax
 - Massive hemoperitoneum
 - Mechanically unstable pelvis fracture with bleeding
 - Extremity blood loss
- Cardiogenic shock
 - Cardiac tamponade
- Neurogenic shock

Disability

- Intracranial hemorrhage/mass lesion
- Cervical spine injury

Patients who have an abnormal voice, abnormal breathing sounds, tachypnea, or altered mental status require further airway evaluation. Blood, vomit, the tongue, foreign objects, and soft tissue swelling can cause airway obstruction; suctioning affords immediate relief in many patients. In the comatose patient, the tongue may fall backward and obstruct the hypopharynx; this can be relieved by either a chin lift or jaw thrust. An oral airway or a nasal trumpet is also helpful in maintaining airway patency, although the former is not usually tolerated by an awake patient. Establishing a definitive airway (i.e., endotracheal intubation) is indicated in patients with apnea; inability to protect the airway due to altered mental status; impending airway compromise due to inhalation injury, hematoma, facial bleeding, soft tissue swelling, or aspiration; and inability to maintain oxygenation. Altered mental status is the most common indication for intubation. Agitation or obtundation, often attributed to intoxication or drug use, may actually be due to hypoxia.

Options for endotracheal intubation include nasotracheal, orotracheal, or operative routes. Nasotracheal intubation can be accomplished only in patients who are breathing spontaneously. Although nasotracheal intubation is frequently used by prehospital providers, the application for this technique in the ED is limited to those patients requiring emergent airway support in whom chemical paralysis cannot be used. Orotracheal intubation is the preferred technique used to establish a definitive airway. Because all patients are presumed to have cervical spine injuries, manual in-line cervical immobilization is essential.⁶ Correct endotracheal placement is verified with 3▶ direct laryngoscopy, capnography, audible bilateral breath sounds, and finally a chest film. The GlideScope®, a video laryngoscope that uses fiber optics to visualize the vocal cords, is being employed more frequently.⁹ Advantages of orotracheal intubation include the direct visualization of the vocal cords, ability to use larger-diameter endotracheal tubes, and applicability to apneic patients. The disadvantage of orotracheal

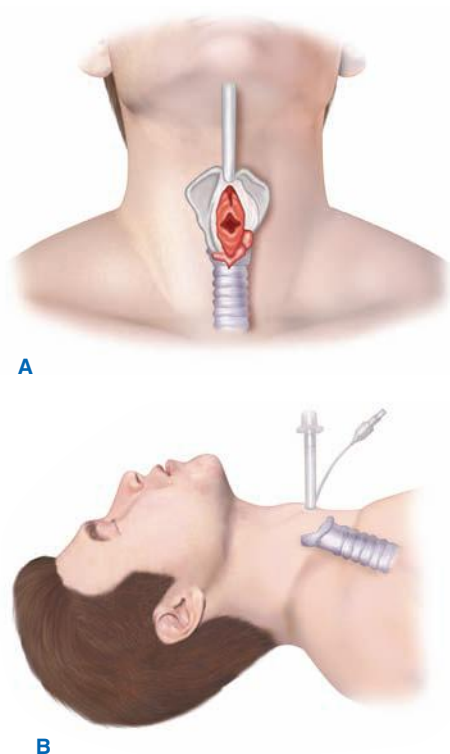


Figure 7-1. Cricothyroidotomy is recommended for emergent surgical establishment of a patent airway. A vertical skin incision avoids injury to the anterior jugular veins, which are located just lateral to the midline. Hemorrhage from these vessels obscures vision and prolongs the procedure. When a transverse incision is made in the cricothyroid membrane, the blade of the knife should be angled inferiorly to avoid injury to the vocal cords. **A.** Use of a tracheostomy hook stabilizes the thyroid cartilage and facilitates tube insertion. **B.** A 6.0 endotracheal tube is inserted after digital confirmation of airway access.

intubation is that conscious patients usually require neuromuscular blockade, which may result in inability to intubate, aspiration, or medication complications. Those who attempt rapid-sequence induction must be thoroughly familiar with the procedure (see Chap. 13).

Patients in whom attempts at intubation have failed or who are precluded from intubation due to extensive facial injuries require operative establishment of an airway. Cricothyroidotomy (Fig. 7-1) is performed through a generous vertical incision, with sharp division of the subcutaneous tissues. Visualization may be improved by having an assistant retract laterally on the neck incision using army-navy retractors. The cricothyroid membrane is verified by digital palpation and opened in a horizontal direction. The airway may be stabilized before incision of the membrane using a tracheostomy hook; the hook should be placed under the thyroid cartilage to elevate the airway. A 6.0 endotracheal tube (maximum diameter in adults) is then advanced through the cricothyroid opening and sutured into place. In patients under the age of 11, cricothyroidotomy is relatively contraindicated due to the risk of subglottic stenosis, and tracheostomy should be performed.

Emergent tracheostomy is indicated in patients with laryngotracheal separation or laryngeal fractures, in whom cricothyroidotomy may cause further damage or result in complete loss

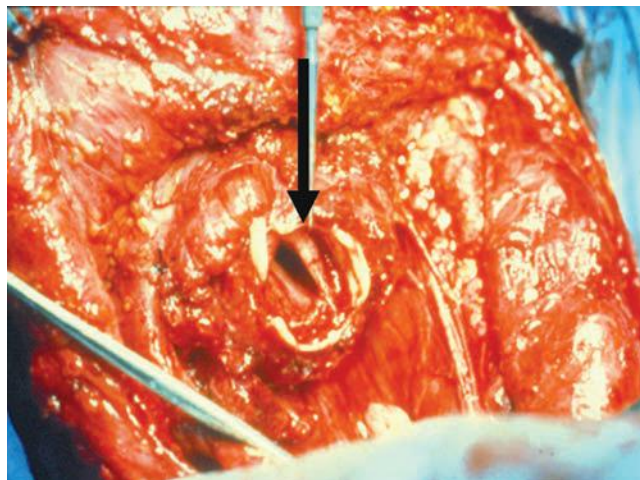


Figure 7-2. A “clothesline” injury can partially or completely transect the anterior neck structures, including the trachea. With complete tracheal transection, the endotracheal tube is placed directly into the distal aperture, with care taken not to push the trachea into the mediastinum.

of the airway. This procedure is best performed in the OR where there is optimal lighting and availability of more equipment (e.g., sternal saw). In these cases, often after a “clothesline” injury, direct visualization and instrumentation of the trachea usually is done through the traumatic anterior neck defect or after a generous collar skin incision (Fig. 7-2). If the trachea is completely transected, a nonpenetrating clamp should be placed on the distal aspect to prevent tracheal retraction into the mediastinum; this is particularly important before placement of the endotracheal tube.

Breathing and Ventilation Once a secure airway is obtained, adequate oxygenation and ventilation must be ensured. All injured patients should receive supplemental oxygen and be monitored by pulse oximetry. The following conditions constitute an immediate threat to life due to inadequate ventilation and should be recognized during the primary survey: tension pneumothorax, open pneumothorax, flail chest with underlying pulmonary contusion, and massive air leak. All of these diagnoses should be made during the initial physical examination.

The diagnosis of tension pneumothorax is presumed in any patient manifesting respiratory distress and hypotension in combination with any of the following physical signs: tracheal deviation away from the affected side, lack of or decreased breath sounds on the affected side, and subcutaneous emphysema on the affected side. Patients may have distended neck veins due to impedance of venous return, but the neck veins may be flat due to concurrent systemic hypovolemia. Tension pneumothorax and simple pneumothorax have similar signs, symptoms, and examination findings, but hypotension qualifies the pneumothorax as a tension pneumothorax. Although immediate needle thoracostomy decompression with a 14-gauge angiocatheter in the second intercostal space in the midclavicular line may be indicated in the field, tube thoracostomy should be performed immediately in the ED before a chest radiograph is obtained (Fig. 7-3). Recent studies suggest the preferred location for needle decompression may be the 5th intercostal space in the anterior axillary line due to body habitus.¹⁰ In cases of tension pneumothorax, the parenchymal tear in the lung acts as a one-way valve, with each inhalation allowing additional air to

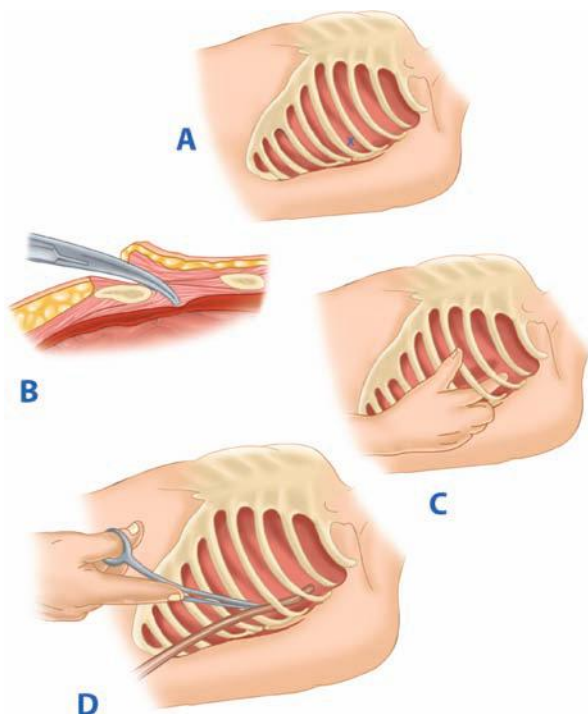


Figure 7-3. **A.** Tube thoracostomy is performed in the midaxillary line at the fourth or fifth intercostal space (inframammary crease) to avoid iatrogenic injury to the liver or spleen. **B.** Heavy scissors are used to cut through the intercostal muscle into the pleural space. This is done on top of the rib to avoid injury to the intercostal bundle located just beneath the rib. **C.** The incision is digitally explored to confirm intrathoracic location and identify pleural adhesions. **D.** A 28F chest tube is directed superiorly and posteriorly with the aid of a large clamp.

accumulate in the pleural space. The normally negative intrapleural pressure becomes positive, which depresses the ipsilateral hemidiaphragm and shifts the mediastinal structures into the contralateral chest. Subsequently, the contralateral lung is compressed and the heart rotates about the superior and inferior vena cava; this decreases venous return and ultimately cardiac output, which culminates in cardiovascular collapse.

An open pneumothorax or “sucking chest wound” occurs with full-thickness loss of the chest wall, permitting free communication between the pleural space and the atmosphere (Fig. 7-4). This compromises ventilation due to equilibration of atmospheric and pleural pressures, which prevents lung inflation and alveolar ventilation, and results in hypoxia and hypercarbia. Complete occlusion of the chest wall defect without a tube thoracostomy may convert an open pneumothorax to a tension pneumothorax. Temporary management of this injury includes covering the wound with an occlusive dressing that is taped on three sides. This acts as a flutter valve, permitting effective ventilation on inspiration while allowing accumulated air to escape from the pleural space on the untaped side, so that a tension pneumothorax is prevented. Definitive treatment requires closure of the chest wall defect and tube thoracostomy remote from the wound.

Flail chest occurs when three or more contiguous ribs are fractured in at least two locations. Paradoxical movement of this free-floating segment of chest wall is usually evident in patients with spontaneous ventilation, due to the negative intrapleural pressure of inspiration. However, the additional work of breathing



A



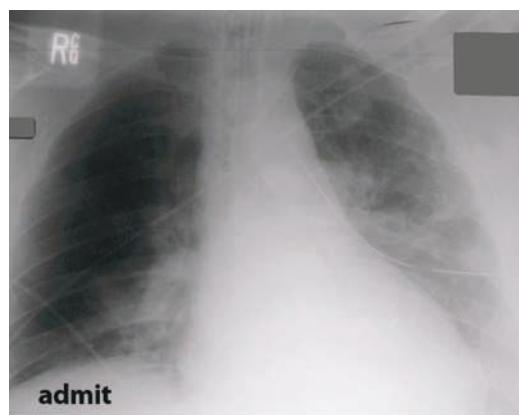
B

Figure 7-4. **A.** Full-thickness loss of the chest wall results in an open pneumothorax. **B.** The defect is temporarily managed with an occlusive dressing that is taped on three sides, which allows accumulated air to escape from the pleural space and thus prevents a tension pneumothorax. Repair of the chest wall defect and tube thoracostomy remote from the wound is definitive treatment.

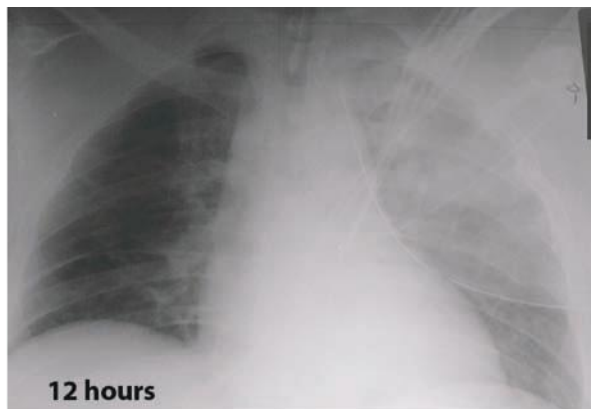
and chest wall pain caused by the flail segment is rarely sufficient to compromise ventilation. Instead, it is the decreased compliance and increased shunt fraction caused by the associated pulmonary contusion that is the source of acute respiratory failure. Pulmonary contusion often progresses during the first 12 hours. Resultant hypoventilation and hypoxemia may require intubation and mechanical ventilation. The patient’s initial chest radiograph often underestimates the extent of the pulmonary parenchymal damage (Fig. 7-5); close monitoring and frequent clinical re-evaluation are warranted.

Massive air leak occurs from major tracheobronchial injuries. Type I injuries are those occurring within 2 cm of the carina.^{11,12} These are often not associated with a pneumothorax due to the envelopment in the mediastinal pleura. Type II injuries are more distal injuries within the tracheobronchial tree and manifest with pneumothorax. Bronchoscopy confirms diagnosis and directs management.

Circulation with Hemorrhage Control With a secure airway and adequate ventilation established, circulatory status is the next priority. An initial approximation of the patient’s cardiovascular



A



B

Figure 7-5. A. Admission chest film may not show the full extent of the patient's pulmonary parenchymal injury. B. This patient's left pulmonary contusion blossomed 12 hours later, and its associated opacity is noted on repeat chest radiograph.

status can be obtained by palpating peripheral pulses. In general, systolic blood pressure (SBP) must be 60 mm Hg for the carotid pulse to be palpable, 70 mm Hg for the femoral pulse, and 80 mm Hg for the radial pulse. Any episode of hypotension (defined as a SBP <90 mm Hg) is assumed to be caused by hemorrhage until proven otherwise. Patients with acute massive blood loss may have paradoxical bradycardia.¹³ Blood pressure and pulse should be measured at least every 5 minutes in patients with significant blood loss until normal vital sign values are restored. High energy auto-pedestrian victims should have their pelvis wrapped with a sheet until radiography can be done.

IV access for fluid resuscitation is obtained with two peripheral catheters, 16-gauge or larger in adults. For patients in whom peripheral angiocatheter access is difficult, intraosseous (IO) needles can be rapidly placed in the proximal tibia of the lower extremity (Fig. 7-6).^{14,15} All medications administered IV may be administered in a similar dosage intraosseously. Although safe for emergent use, the needle should be removed once alternative access is established to prevent osteomyelitis. Blood should be drawn simultaneously for a bedside hemoglobin level and routine trauma laboratory tests. In the seriously injured patient arriving in shock, an arterial blood gas, cross-matching for possible red blood cell (RBC) transfusion, and a coagulation panel should be obtained. In these patients, secondary large bore cannulae should be obtained via the femoral or subclavian

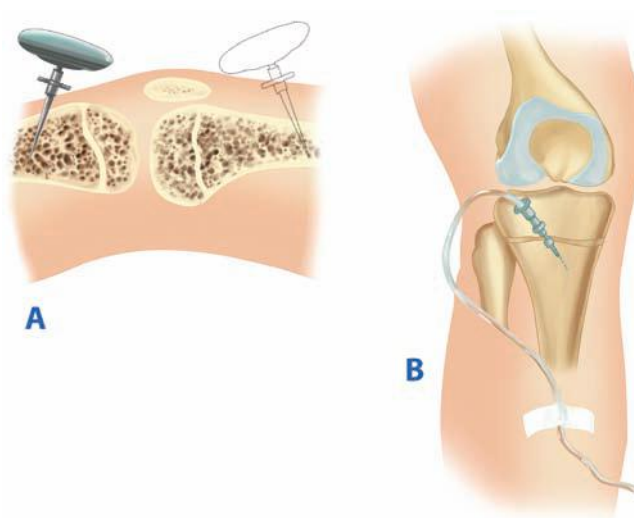


Figure 7-6. Intraosseous infusions are indicated for children <6 years of age in whom one or two attempts at IV access have failed. A. The proximal tibia is the preferred location. Alternatively, the distal femur can be used if the tibia is fractured. B. The needle should be directed away from the epiphyseal plate to avoid injury. The position is satisfactory if bone marrow can be aspirated and saline can be easily infused without evidence of extravasation.

veins, or saphenous vein cutdown; Cordis introducer catheters are preferred over triple-lumen catheters. In general, initial access in trauma patients is best secured in the groin or ankle, so that the catheter will not interfere with the performance of other diagnostic and therapeutic thoracic procedures. Saphenous vein cutdowns at the ankle provide excellent access (Fig. 7-7). The saphenous vein is reliably found 1 cm anterior and 1 cm superior to the medial malleolus. Standard 14-gauge catheters can be quickly placed, even in an exsanguinating patient with

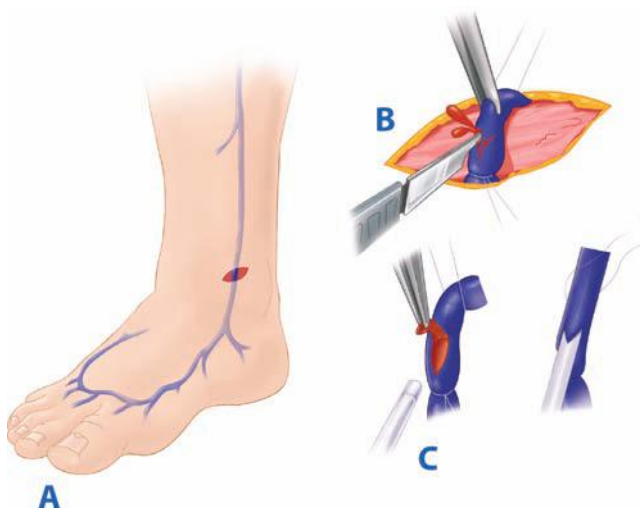


Figure 7-7. Saphenous vein cutdowns are excellent sites for fluid resuscitation access. A. The vein is consistently found 1 cm anterior and 1 cm superior to the medial malleolus. B. Proximal and distal traction sutures are placed with the distal suture ligated. C. A 14-gauge IV catheter is introduced and secured with sutures and tape to prevent dislodgment.

collapsed veins. If IV access cannot be achieved readily, the IO route is very useful, particularly for drug administration.^{14,15} Additional venous access often is obtained through the femoral or subclavian veins with Cordis introducer catheters. A rule of thumb to consider for secondary access is placement of femoral access for thoracic trauma and jugular or subclavian access for abdominal trauma. However, jugular or subclavian catheters provide a more reliable measurement of central venous pressure (CVP), which may be helpful in determining the volume status of the patient and in excluding cardiac tamponade. In severely injured children < 6 years of age, the preferred venous access is peripheral intravenous catheters followed by an IO needle. Central venous catheter placement or saphenous vein cutdown may be considered as the third choice of access based upon provider experience. Inadvertent femoral artery cannulation, however, may result in limb-threatening distal arterial spasm.

External control of any visible hemorrhage should be achieved promptly while circulating volume is restored. Manual compression of open wounds with ongoing bleeding should be done with a single 4 × 4 gauze and a gloved hand. Covering the wound with excessive dressings may permit ongoing unrecognized blood loss that is hidden underneath the dressing. Blind clamping of bleeding vessels should be avoided because of the risk to adjacent structures, including nerves. This is particularly true for penetrating injuries of the neck, thoracic outlet, and groin, where bleeding may be torrential and arising deep within the wound. In these situations, a gloved finger is placed through the wound directly onto the bleeding vessel and enough pressure is applied to control active bleeding. The surgeon performing this maneuver must then walk with the patient to the OR for definitive treatment. For bleeding of the extremities it is tempting to apply tourniquets for hemorrhage control, but digital occlusion will usually control the bleeding, and complete vascular occlusion risks permanent neuromuscular impairment. Patients in shock have a lower tolerance to warm ischemia, and an occluded extremity is prone to small vessel thrombosis.

For patients with open fractures, fracture reduction with stabilization via splints will limit bleeding both externally and into the subcutaneous tissues. Scalp lacerations through the galea aponeurotica tend to bleed profusely; these can be temporarily controlled with skin staples, Raney clips, or a large full-thickness continuous running nylon stitch.

During the circulation section of the primary survey, four life-threatening injuries must be identified promptly: (a) massive hemothorax, (b) cardiac tamponade, (c) massive hemoperitoneum, and (d) mechanically unstable pelvic fractures with bleeding. Massive hemoperitoneum and mechanically unstable pelvic fractures are discussed in “Emergent Abdominal Exploration” and “Pelvic Fractures and Emergent Hemorrhage Control,” respectively. Three critical tools used to differentiate these in the multisystem trauma patient are chest radiograph, pelvis radiograph, and focused abdominal sonography for trauma (FAST) (see “Regional Assessment and Special Diagnostic Tests”). A massive hemothorax (life-threatening injury number one) is defined as >1500 mL of blood or, in the pediatric population, >25% of the patient’s blood volume in the pleural space (Fig. 7-8). Although it may be estimated on chest radiograph, tube thoracostomy is the only reliable means to quantify the amount of hemothorax. After blunt trauma, a major hemothorax usually is due to multiple rib fractures with severed intercostal arteries, but occasionally bleeding is from lacerated lung parenchyma which is usually associated with an air leak. After penetrating trauma, a great vessel or pulmonary hilar vessel injury should be presumed. In either scenario, a massive hemothorax is an indication for operative intervention, but tube thoracostomy is critical to facilitate lung re-expansion, which may improve oxygenation and cardiac performance as well as tamponade venous bleeding.

Cardiac tamponade (life-threatening injury number two) occurs most commonly after penetrating thoracic wounds, although occasionally blunt rupture of the heart, particularly the atrial appendage, is seen. Acutely, <100 mL of pericardial

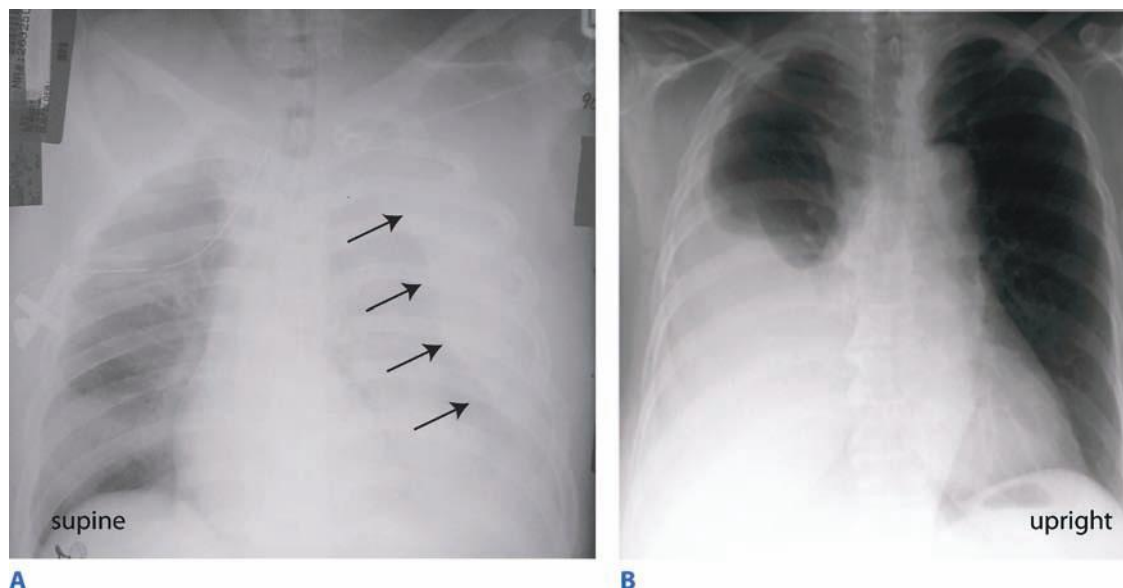


Figure 7-8. More than 1500 mL of blood in the pleural space is considered a massive hemothorax. Chest film findings reflect the positioning of the patient. **A.** In the supine position, blood tracks along the entire posterior section of the chest and is most notable pushing the lung away from the chest wall. **B.** In the upright position, blood is visible dependently in the right pleural space.

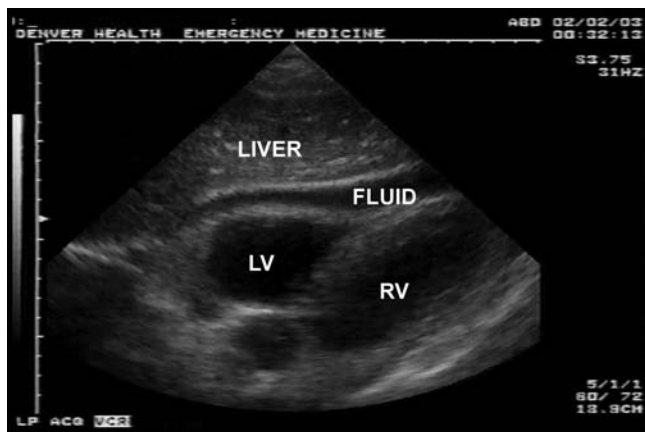


Figure 7-9. Subxiphoid pericardial ultrasound reveals a large pericardial fluid collection.

blood may cause pericardial tamponade.¹⁶ The classic Beck's triad—dilated neck veins, muffled heart tones, and a decline in arterial pressure—is usually not appreciated in the trauma bay because of the noisy environment and associated hypovolemia. Because the pericardium is not acutely distensible, the pressure in the pericardial sac will rise to match that of the injured chamber. When this pressure exceeds that of the right atrium, right atrial filling is impaired and right ventricular preload is reduced. This ultimately leads to decreased right ventricular output. Additionally, increased intrapericardial pressure impedes myocardial blood flow, which leads to subendocardial ischemia and a further reduction in cardiac output.

Diagnosis of hemopericardium is best achieved by bedside ultrasound of the pericardium (Fig. 7-9). Early in the course of tamponade, blood pressure and cardiac output will transiently improve with fluid administration due to increased central venous pressure. In patients with any hemodynamic disturbance, a pericardial drain is placed using ultrasound guidance (Fig. 7-10). Removing as little as 15 to 20 mL of blood will often temporarily stabilize the patient's hemodynamic status,

Table 7-2

Current indications and contraindications for emergency department thoracotomy

Indications

Salvageable postinjury cardiac arrest:

- Patients sustaining witnessed penetrating trauma to the torso with <15 min of prehospital CPR
- Patients sustaining witnessed blunt trauma with <10 min of prehospital CPR
- Patients sustaining witnessed penetrating trauma to the neck or extremities with <5 min of prehospital CPR

Persistent severe postinjury hypotension (SBP \leq 60 mm Hg) due to:

- Cardiac tamponade
- Hemorrhage—intrathoracic, intra-abdominal, extremity, cervical
- Air embolism

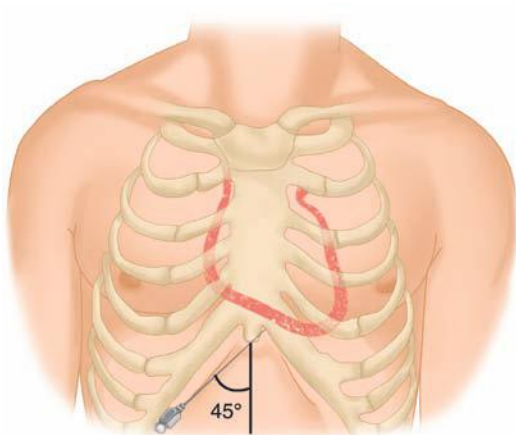
Contraindications

- Penetrating trauma: CPR >15 min and no signs of life (pupillary response, respiratory effort, motor activity)
- Blunt trauma: CPR >10 min and no signs of life or asystole without associated tamponade

CPR = cardiopulmonary resuscitation; SBP = systolic blood pressure.

and alleviate subendocardial ischemia with associated lethal arrhythmias, and allow safe transport to the OR for sternotomy. Pericardiocentesis is successful in decompressing tamponade in approximately 80% of cases; the majority of failures are due to the presence of clotted blood within the pericardium. Patients with a SBP <60 mm Hg warrant resuscitative thoracotomy (RT) with opening of the pericardium for rapid decompression and to address the injury.

The utility of RT has been debated for decades. Current indications are based on 30 years of prospective data, supported by a recent multicenter prospective study (Table 7-2).^{17,18} RT



A



B

Figure 7-10. Pericardiocentesis is indicated for patients with evidence of pericardial tamponade. **A.** Access to the pericardium is obtained through a subxiphoid approach, with the needle angled 45 degrees up from the chest wall and toward the left shoulder. **B.** Seldinger technique is used to place a pigtail catheter. Blood can be repeatedly aspirated with a syringe or the tubing may be attached to a gravity drain. Evacuation of unclogged pericardial blood prevents subendocardial ischemia and stabilizes the patient for transport to the operating room for sternotomy.

is associated with the highest survival rate after isolated cardiac injury; 35% of patients presenting in shock and 20% without vital signs (i.e., no pulse or obtainable blood pressure) are salvaged after isolated penetrating injury to the heart. For all penetrating wounds, survival rate is 15%. Conversely, patient outcome is poor when RT is done for blunt trauma, with 2% survival among patients in shock and <1% survival among those with no vital signs. Thus, patients undergoing cardiopulmonary resuscitation upon arrival to the ED should undergo RT selectively based on injury and transport time (Fig. 7-11). RT is best accomplished using a generous left anterolateral thoracotomy, with the skin incision started to the right of the sternum (Fig. 7-12). A longitudinal pericardiotomy anterior to the phrenic nerve is used to release cardiac tamponade and permits access to the heart for cardiac repair and open cardiac massage. Cross-clamping of the aorta improves central circulation, augments cerebral and coronary blood flow, and limits further abdominal blood loss (Fig. 7-13). The patient must sustain a SBP of 70 mm Hg after RT and associated interventions to be considered resuscitatable, and hence transported to the OR.^{17,18}

Disability and Exposure The Glasgow coma scale (GCS) score should be determined for all injured patients (Table 7-3). It is calculated by adding the scores of the best motor response, best verbal response, and the best eye response. Scores range from 3 (the lowest) to 15 (normal). Scores of 13 to 15 indicate mild head injury, 9 to 12 moderate injury, and ≤ 8 severe injury.

The GCS is a quantifiable determination of neurologic function that is useful for triage, treatment, and prognosis.

Neurologic evaluation is critical before administration of neuromuscular blockade for intubation. Subtle changes in mental status can be caused by hypoxia, hypercarbia, or hypovolemia, or may be an early sign of increasing intracranial pressure. An abnormal mental status should prompt an immediate re-evaluation of the ABCs and consideration of central nervous system injury. Deterioration in mental status may be subtle and may not progress in a predictable fashion. For example, previously calm, cooperative patients may become anxious and combative as they become hypoxic. However, a patient who is agitated and combative from drugs or alcohol may become somnolent if hypovolemic shock develops. Patients with neurogenic shock are typified by hypotension with relative bradycardia, and are often first recognized due to paralysis, decreased rectal tone or priapism. Patients with high spinal cord disruption are at greatest risk for neurogenic shock due to physiologic disruption of sympathetic fibers; treatment consists of volume loading and a dopamine infusion which is both inotropic and chronotropic. Seriously injured patients must have all of their clothing removed to avoid overlooking limb- or life-threatening injuries.

Shock Classification and Initial Fluid Resuscitation Classic signs and symptoms of shock are tachycardia, hypotension, tachypnea, altered mental status, diaphoresis, and pallor (Table 7-4). In general, the quantity of acute blood loss correlates

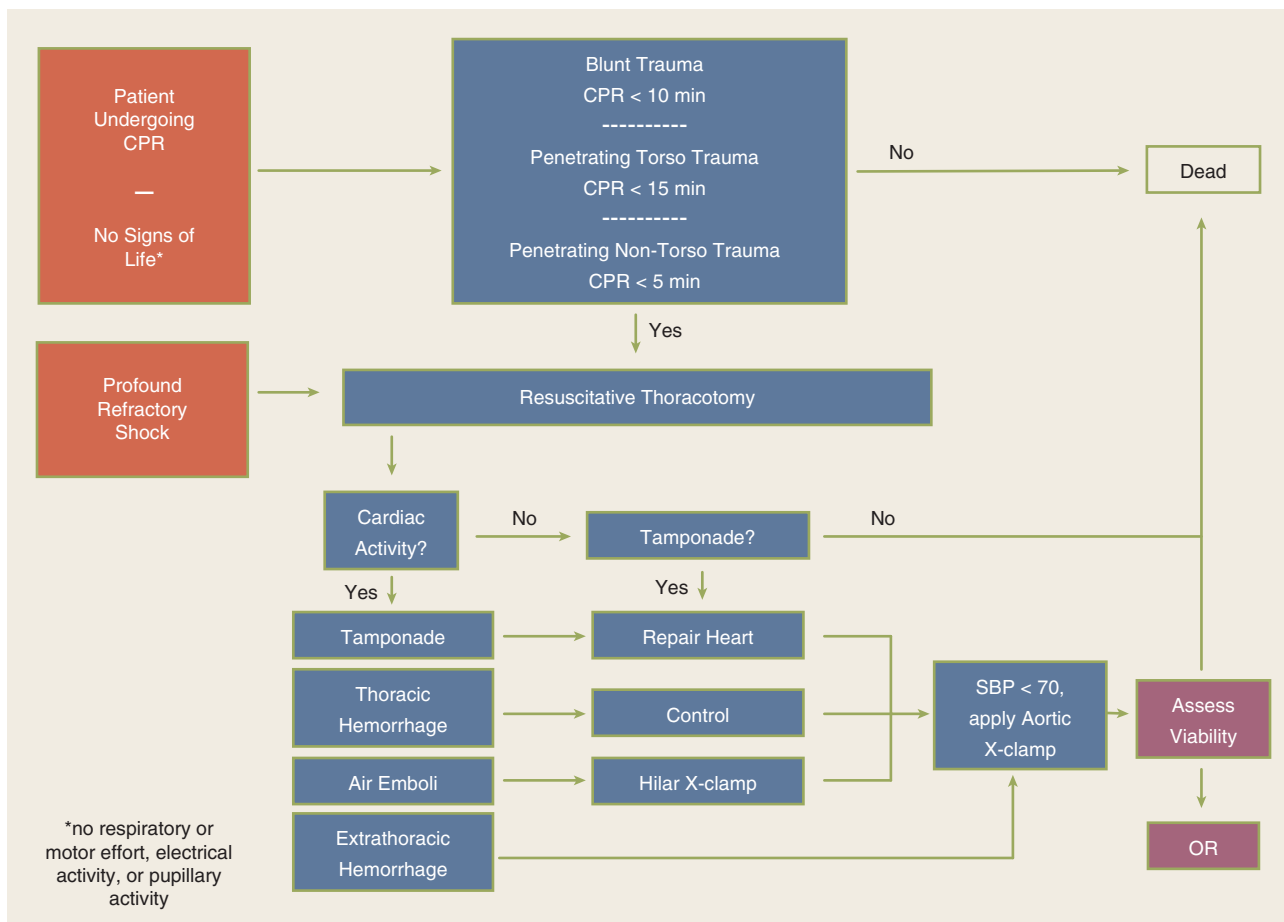


Figure 7-11. Algorithm directing the use of resuscitative thoracotomy (RT) in the injured patient undergoing cardiopulmonary resuscitation (CPR). ECG = electrocardiogram; OR = operating room; SBP = systolic blood pressure.

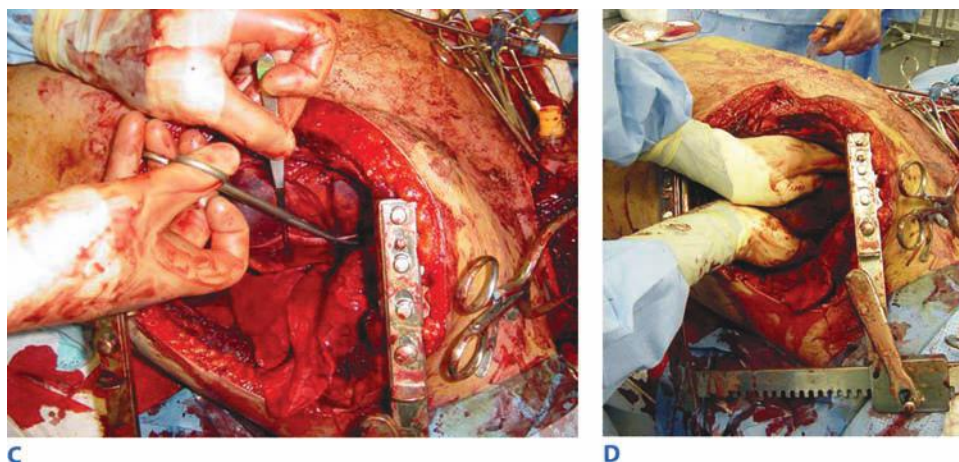
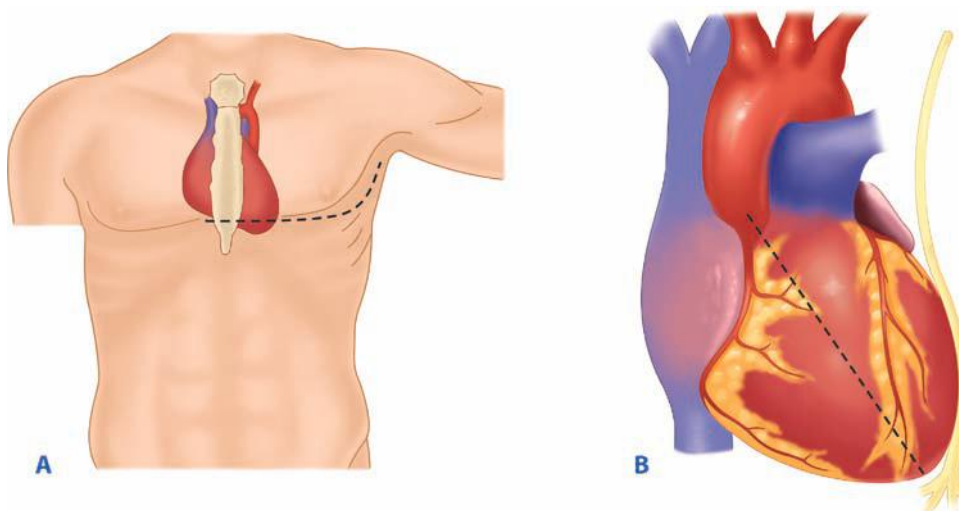


Figure 7-12. A. Resuscitative thoracotomy (RT) is performed through the fifth intercostal space using the anterolateral approach. B and C. The pericardium is opened anterior to the phrenic nerve, and the heart is rotated out for evaluation. D. Open cardiac massage should be performed with a hinged, clapping motion of the hands, with sequential closing from palms to fingers. The two-handed technique is strongly recommended because the one-handed massage technique poses the risk of myocardial perforation with the thumb.

with physiologic abnormalities. For example, patients in class II shock are tachycardic but they do not exhibit a reduction in blood pressure until over 1500 mL of blood loss, or class III shock. Physical findings should be used as an aid in the evaluation of the patient's response to treatment. The goal of fluid resuscitation is to re-establish tissue perfusion. Fluid resuscitation begins with a 2 L (adult) or 20 mL/kg (child) IV bolus

of isotonic crystalloid, typically Ringer's lactate. For persistent hypotension (SBP <90 mm Hg in an adult), the current trend is to activate a massive transfusion protocol (MTP) in which red blood cells (RBC) and fresh-frozen plasma (FFP) are administered early. The details of a MTP are discussed later. Patients who have a good response to fluid infusion (i.e., normalization of vital signs, clearing of the sensorium) and evidence of good

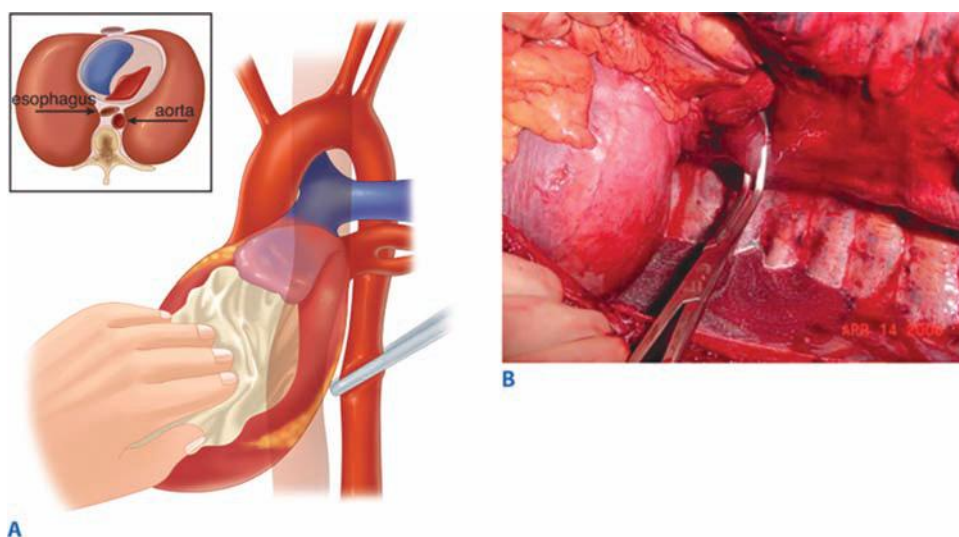


Figure 7-13. Aortic cross-clamp is applied with the left lung retracted superiorly, below the inferior pulmonary ligament, just above the diaphragm. The flaccid aorta is identified as the first structure encountered on top of the spine when approached from the left chest.

Table 7-3

Glasgow coma scale^a

		ADULTS	INFANTS/CHILDREN
Eye opening	4	Spontaneous	Spontaneous
	3	To voice	To voice
	2	To pain	To pain
	1	None	None
Verbal	5	Oriented	Alert, normal vocalization
	4	Confused	Cries, but consolable
	3	Inappropriate words	Persistently irritable
	2	Incomprehensible words	Restless, agitated, moaning
	1	None	None
Motor response	6	Obeys commands	Spontaneous, purposeful
	5	Localizes pain	Localizes pain
	4	Withdraws	Withdraws
	3	Abnormal flexion	Abnormal flexion
	2	Abnormal extension	Abnormal extension
	1	None	None

^aScore is calculated by adding the scores of the best motor response, best verbal response, and eye opening. Scores range from 3 (the lowest) to 15 (normal).

peripheral perfusion (warm fingers and toes with normal capillary refill) are presumed to have adequate overall perfusion. Urine output is a quantitative, reliable indicator of organ perfusion. Adequate urine output is 0.5 mL/kg per hour in an adult, 1 mL/kg per hour in a child, and 2 mL/kg per hour in an infant <1 year of age. Because measurement of this resuscitation-related variable is time dependent, it is generally more useful in the OR and intensive care unit (ICU) setting, than in initial evaluation in the trauma bay.

There are several caveats to be considered when evaluating the injured patient for shock. Tachycardia is often the earliest sign of ongoing blood loss, but the critical issue is change over time. Furthermore, individuals in good physical condition with a resting pulse rate in the fifties may manifest a relative tachycardia in the nineties; although clinically significant, this does

not meet the standard definition of tachycardia. Conversely, patients receiving cardiac medications such as beta blockers may not be capable of increasing their heart rate to compensate for hypovolemia. Bradycardia can occur with rapid severe blood loss¹³; this is an ominous sign, often heralding impending cardiovascular collapse. Other physiologic stresses, aside from hypovolemia, may produce tachycardia, such as hypoxia, pain, anxiety, and stimulant drugs (cocaine, amphetamines). As noted previously, decreased SBP is not a reliable early sign of hypovolemia, because blood loss must exceed 30% before hypotension occurs. Additionally, younger patients may maintain their SBP due to sympathetic tone despite severe intravascular deficits until they are on the verge of cardiac arrest. Pregnant patients have a progressive increase in circulating blood volume over gestation; therefore, they must lose a relatively larger volume of

Table 7-4

Signs and symptoms of advancing stages of hemorrhagic shock

	CLASS I	CLASS II	CLASS III	CLASS IV
Blood loss (mL)	Up to 750	750–1500	1500–2000	>2000
Blood loss (%BV)	Up to 15%	15%–30%	30%–40%	>40%
Pulse rate	<100	>100	>120	>140
Blood pressure	Normal	Normal	Decreased	Decreased
Pulse pressure (mm Hg)	Normal or increased	Decreased	Decreased	Decreased
Respiratory rate	14–20	>20–30	30–40	>35
Urine output (mL/h)	>30	>20–30	5–15	Negligible
CNS/mental status	Slightly anxious	Mildly anxious	Anxious and confused	Confused and lethargic

BV = blood volume; CNS = central nervous system.

blood before manifesting signs and symptoms of hypovolemia (see *Special Trauma Populations*).

Based on the initial response to fluid resuscitation, hypovolemic injured patients can be separated into three broad categories: responders, transient responders, and nonresponders. Individuals who are stable or have a good response to the initial fluid therapy as evidenced by normalization of vital signs, mental status, and urine output are unlikely to have significant ongoing hemorrhage, and further diagnostic evaluation for occult injuries can proceed in an orderly fashion (see “Secondary Survey”). At the other end of the spectrum are patients classified as “nonresponders” who have persistent hypotension despite aggressive resuscitation. These patients mandate immediate identification of the source of hypotension with appropriate intervention to prevent a fatal outcome. Transient responders are those who respond initially to volume loading with improvement in vital signs, but then deteriorate hemodynamically again. This group of patients can be challenging to triage for definitive management.

Persistent Hypotension Patients with ongoing hemodynamic instability, whether “nonresponders” or “transient responders,”

4▶ require systematic evaluation and prompt intervention. The spectrum of disease in patients with persistent hypotension ranges from overwhelming multisystem injury to easily reversible problems such as a tension pneumothorax. One must first consider the four categories of shock that may be the underlying cause: hemorrhagic, cardiogenic, neurogenic, and septic. In patients with persistent hypotension and tachycardia, cardiogenic or hemorrhagic shock are the likely causes. Ultrasound evaluation of the pericardium, pleural cavities, and abdomen in combination with plain radiographs of the chest and pelvis will usually identify the source of hemorrhagic and/or cardiogenic shock. Evaluation of the CVP may further assist in distinguishing between these two categories. A patient with distended neck veins and a CVP of >15 cm H_2O is likely to be in cardiogenic shock. The CVP may be falsely elevated, however, if the patient is agitated and straining, or fluid administration is overzealous; isolated readings must be interpreted with caution. A patient with flat neck veins and a CVP of <5 cm H_2O is likely hypovolemic due to ongoing hemorrhage. Serial base deficit measurements are helpful; a persistent base arterial deficit of >8 mmol/L implies ongoing cellular shock.^{19,20} Serum lactate is also used to monitor the patient’s physiologic response to resuscitation.²¹ Evolving technology, such as near infrared spectroscopy, may provide noninvasive monitoring of oxygen delivery to tissue.²² Except for patients transferred from outside facilities >12 hours after injury, few patients present in septic shock in the trauma bay. Patients with neurogenic shock as a component of hemodynamic instability often are recognized during the disability section of the primary survey to have paralysis, but those patients chemically paralyzed before physical examination may be misdiagnosed.

The differential diagnosis of cardiogenic shock in trauma patients is: (a) tension pneumothorax, (b) pericardial tamponade, (c) blunt cardiac injury, (d) myocardial infarction, and (e) bronchovenous air embolism. Tension pneumothorax, the most frequent cause of cardiac failure, and pericardial tamponade have been discussed earlier. Although as many as one-third of patients sustaining significant blunt chest trauma experience some degree of blunt cardiac injury, few such injuries result in hemodynamic embarrassment. Patients with electrocardiographic

(ECG) abnormalities or dysrhythmias require continuous ECG monitoring and antidysrhythmic treatment as needed. Unless myocardial infarction is suspected, there is no role for routine serial measurement of cardiac enzyme levels—they lack specificity and do not predict significant dysrhythmias.²³ In patients who have no identified injuries who are being considered for discharge from the ED, the combination of a normal EKG and troponin level at admission and 8 hours later, rules out significant blunt cardiac injury.²⁴ The patient with hemodynamic instability requires appropriate resuscitation and may benefit from hemodynamic monitoring to optimize preload and guide inotropic support. Echocardiography (ECHO) is performed to exclude valvular or septal injuries, and the most common finding is right ventricular dyskinesia due to the anterior orientation of the right versus left ventricle. Transthoracic and transesophageal ECHO are now becoming routine in many surgical intensive care units (SICUs).^{25,26} Patients with refractory cardiogenic shock may occasionally require placement of an intra-aortic balloon pump to decrease myocardial work and enhance coronary perfusion. Acute myocardial infarction may be the cause of a motor vehicle collision or other trauma in older patients. Although optimal initial management includes treatment for the evolving infarction, such as lytic therapy and emergent angioplasty, these decisions must be individualized in accordance with the patient’s other injuries.

Air embolism is a frequently overlooked lethal complication of pulmonary injury. Air emboli can occur after blunt or penetrating trauma, where air from an injured bronchus enters an adjacent injured pulmonary vein (bronchovenous fistula) and returns air to the left heart. Air accumulation in the left ventricle impedes diastolic filling, and during systole air is pumped into the coronary arteries, disrupting coronary perfusion. The typical case is a patient with a penetrating thoracic injury who is hemodynamically stable but experiences cardiac arrest after being intubated and placed on positive pressure ventilation. The patient should immediately be placed in Trendelenburg’s position to trap the air in the apex of the left ventricle. Emergency thoracotomy is followed by cross-clamping of the pulmonary hilum on the side of the injury to prevent further introduction of air (Fig. 7-14). Air is aspirated from the apex of the left ventricle and then the aortic root with an 18-gauge needle and 50-mL syringe. Vigorous massage is used to force the air bubbles through the coronary arteries; if this is unsuccessful, a tuberculin syringe is used to aspirate air bubbles from the right coronary artery. Once circulation is restored, the patient should be kept in Trendelenburg’s position with the pulmonary hilum clamped until the pulmonary venous injury is controlled operatively.

Persistent hypotension due to uncontrolled hemorrhage is associated with high mortality. A rapid search for the source or sources of hemorrhage includes visual inspection with knowledge of the injury mechanism, FAST, and chest and pelvic radiographs. During diagnostic evaluation, type O RBCs (O-negative for women of childbearing age) and thawed AB plasma should be administered at a ratio of 2:1. Type-specific RBCs should be administered as soon as available. The acute coagulopathy of trauma is now well recognized, and underscores the importance of pre-emptive blood component administration. The resurgent interest in viscoelastic hemostatic assays (thrombelastography [TEG] and thrombelastometry [ROTEM]) has facilitated the appropriate and timely use of clotting adjuncts, including the prompt recognition of fibrinolysis. In patients with clear indications for operation, essential films should be taken and the

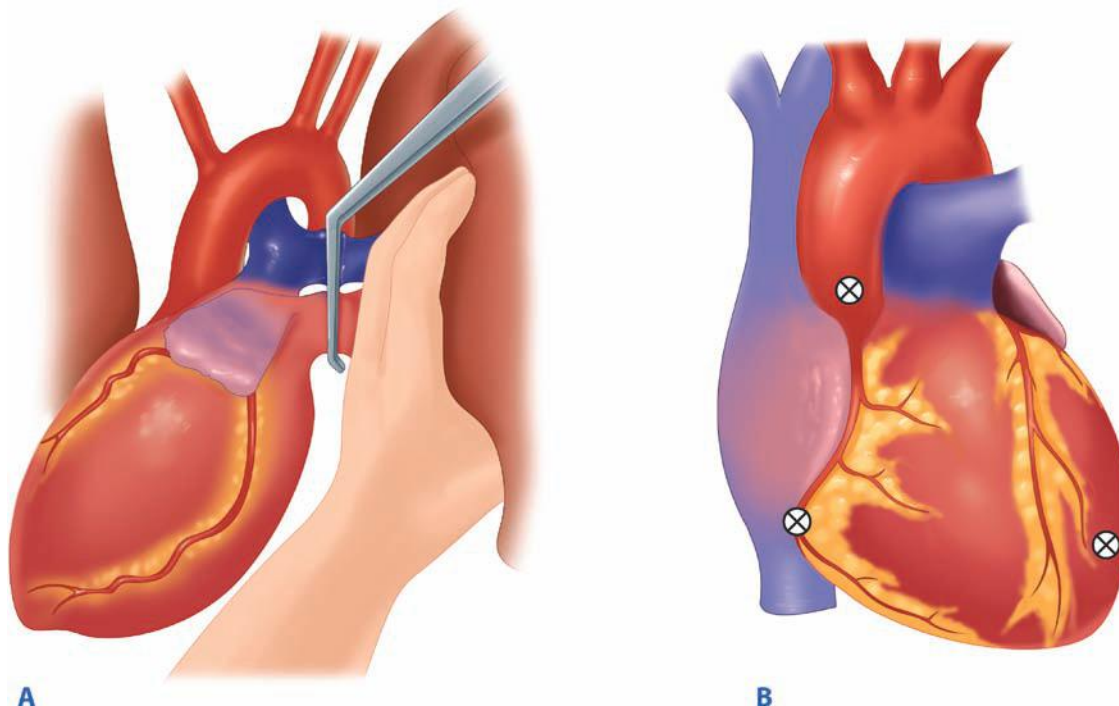


Figure 7-14. **A.** A Satinsky clamp is used to clamp the pulmonary hilum to prevent further bronchovenous air embolism. **B.** Sequential sites of aspiration include the left ventricle, the aortic root, and the right coronary artery.

patient transported to the OR immediately. Such patients include those with blunt trauma and massive hemothorax, those with penetrating trauma and an initial chest tube output of >1 L, and those with abdominal trauma and ultrasound evidence of extensive hemoperitoneum. In patients with gunshot wounds to the chest or abdomen, a chest and abdominal film, with radiopaque markers at the wound sites, should be obtained to determine the trajectory of the bullet or location of a retained fragment. For example, a patient with a gunshot wound to the upper abdomen should have a chest radiograph to ensure that the bullet did not traverse the diaphragm causing intrathoracic injury. Similarly, a chest radiograph is important in a patient with a gunshot wound to the right chest to evaluate the left hemithorax. If a patient arrives with a penetrating weapon remaining in place, the weapon should *not* be removed in the ED, because it could be tamponading a lacerated blood vessel (Fig. 7-15). The surgeon should extract the offending instrument in the controlled

environment of the OR, ideally once an incision has been made with adequate exposure. In situations where knives are embedded in the head or neck, preoperative imaging may be useful to anticipate arterial injuries.

In patients without clear operative indications and persistent hypotension, one should systematically evaluate the five potential sources of blood loss: scalp, chest, abdomen, pelvis, and extremities. Significant bleeding at the scene may be noted by paramedics, but its quantification is unreliable. Examination should seek active bleeding from a scalp laceration that may be readily controlled with clips or staples. Thoracoabdominal trauma should be evaluated with a combination of chest radiograph, FAST, and pelvic radiograph. If the FAST results are negative and no other source of hypotension is obvious, diagnostic peritoneal aspiration should be entertained.²⁷ Extremity examination and radiographs should be used to search for associated fractures. Fracture-related blood loss, when additive, may



Figure 7-15. If a weapon is still in place, it should be removed in the operating room, because it could be tamponading a lacerated blood vessel.

be a potential source of the patient's hemodynamic instability. Each rib fracture can produce 100 to 200 mL of blood loss; for tibial fractures, 300 to 500 mL; for femur fractures, 800 to 1000 mL; and for pelvic fractures >2000 mL. Although no single injury can account for the patient's hemodynamic instability, the sum of the injuries may result in life-threatening blood loss. The diagnostic measures advocated earlier are those that can be easily performed in the trauma bay. Transport of a hypotensive patient out of the ED for computed tomographic (CT) scanning is hazardous; monitoring is compromised, and the environment is suboptimal for dealing with acute problems. The surgeon must accompany the patient and be prepared to abort the CT scan with diversion to the OR. This dilemma is becoming less common in many trauma centers where CT scanning is done in the ED.

The concept of hypotensive resuscitation in the ED remains controversial, and it is primarily relevant for patients with penetrating vascular injuries. Experimental work suggests that an endogenous sealing clot of an injured artery may be disrupted at an SBP of >90 mm Hg²⁸; thus, many believe that this should be the preoperative blood pressure target for patients with potential torso arterial injuries. On the other hand, optimal management of traumatic brain injury (TBI) includes maintaining the SBP >100 mm Hg,²⁹ and thus, hypotensive resuscitation is not appropriate for most blunt trauma patients.

Secondary Survey

Once the immediate threats to life have been addressed, a thorough history is obtained and the patient is examined in a systematic fashion. The patient and surrogates should be queried to obtain an AMPLE history (Allergies, Medications, Past illnesses or Pregnancy, Last meal, and Events related to the injury). The physical examination should be literally head to toe, with special attention to the patient's back, axillae, and perineum, because injuries here are easily overlooked. All potentially seriously injured patients should undergo digital rectal examination to evaluate for sphincter tone, presence of blood, rectal perforation, or a high-riding prostate; this is particularly critical in patients with suspected spinal cord injury, pelvic fracture, or transpelvic gunshot wounds. Vaginal examination with a speculum should be performed in women with pelvic fractures to exclude an open fracture. Specific injuries, their associated signs and symptoms, diagnostic options, and treatments are discussed in detail later in this chapter.

Adjuncts to the physical examination include vital sign and CVP monitoring, ECG monitoring, nasogastric tube placement, Foley catheter placement, radiographs, hemoglobin, urinalysis, and base deficit measurements, and repeat FAST exam. A nasogastric tube should be inserted in all intubated patients to decrease the risk of gastric aspiration but may not be necessary in the awake patient. Nasogastric tube placement in patients with complex mid-facial fractures is contraindicated; rather, a tube should be placed orally if required. Nasogastric tube evaluation of stomach contents for blood may suggest occult gastroduodenal injury or the errant path of the nasogastric tube on a chest film may indicate a left diaphragm injury. A Foley catheter should be inserted in patients unable to void to decompress the bladder, obtain a urine specimen, and monitor urine output. Gross hematuria demands evaluation of the genitourinary system for injury. Foley catheter placement should be deferred until urologic evaluation in patients with signs of urethral injury: blood at the meatus, perineal or scrotal hematomas, or a high-riding prostate. Although policies vary at individual institutions,

most agree patients in extremis with need for Foley catheter placement should undergo one attempt at catheterization; if the catheter does not pass easily, a percutaneous suprapubic cystostomy should be considered.

Selective radiography and laboratory tests are done early in the evaluation after the primary survey. For patients with severe blunt trauma, chest and pelvic radiographs should be obtained. Historically, a lateral cervical spine radiograph was also obtained, hence the reference to *the big three* films, but currently patients preferentially undergo CT scanning of the spine rather than plain film radiography. For patients with truncal gunshot wounds, anteroposterior and at times lateral radiographs of the chest and abdomen are warranted. It is important to mark the entrance and exit sites of penetrating wounds with ECG pads, metallic clips, or staples so that the trajectory of the missile can be estimated. Limited one-shot extremity radiographs also may be taken. In critically injured patients, blood samples for a routine trauma panel (type and cross-match, complete blood count, blood chemistries, coagulation studies, and arterial blood gas analysis) should be sent to the laboratory. For less severely injured patients only a complete blood count and urinalysis may be required. Because older patients may present in subclinical shock, even with minor injuries, routine analysis of an arterial blood gas in patients over the age of 55 should be considered. Repeat FAST is performed if there are any signs of abdominal injury or unexplained blood loss.

Many trauma patients cannot provide specific information about the mechanism of their injury. Emergency medical service personnel and police are trained to evaluate an injury scene and should be questioned while they are present in the ED. For automobile collisions, the speed of the vehicles involved, angle of impact, use of restraints, airbag deployment, condition of the steering wheel and windshield, amount of intrusion, ejection of the patient from the vehicle, and fate of other passengers should be ascertained. For other injury mechanisms, critical information includes such things as height of a fall, surface impact, helmet use, and weight of an object by which the patient was crushed. In patients sustaining gunshot wounds, velocity, caliber, distance, and presumed path of the bullet are important, if known. For patients with stab wounds, the length and type of object is helpful. Finally, some patients experience a combination of blunt and penetrating trauma. Do not assume that someone who was stabbed was not also assaulted; the patient may have a multitude of injuries and cannot be presumed to have only injuries associated with the more obvious penetrating mechanism. In short, these details of information are critical to the clinician to determine overall mechanism of injury and anticipate its associated injury patterns.

Mechanisms and Patterns of Injury

In general, more energy is transferred over a wider area during blunt trauma than from a penetrating wound. As a result, blunt trauma is associated with multiple widely distributed injuries, whereas in penetrating wounds the damage is localized to the path of the bullet or knife. In blunt trauma, organs that cannot yield to impact by elastic deformation are most likely to be injured, namely, the solid organs (liver, spleen, and kidneys). For penetrating trauma, organs with the largest surface area when viewed from the front are most prone to injury (small bowel, liver, and colon). Additionally, because bullets and knives usually follow straight lines, adjacent structures are commonly injured (e.g., the pancreas and duodenum).

Trauma surgeons often separate patients who have sustained blunt trauma into categories according to their risk for multiple injuries: those sustaining high energy transfer injuries and those sustaining low energy transfer injuries. Injuries involving high energy transfer include auto-pedestrian accidents, motor vehicle collisions in which the car's change of velocity (ΔV) exceeds 20 mph or in which the patient has been ejected, motorcycle collisions, and falls from heights >20 ft.³⁰ In fact, for motor vehicle accidents the variables strongly associated with life-threatening injuries, and hence reflective of the magnitude of the mechanism, are death of another occupant in the vehicle, extrication time of >20 minutes, ΔV >20 mph, lack of restraint use, and lateral impact.³⁰ Low-energy trauma, such as being struck with a club or falling from a bicycle, usually does not result in widely distributed injuries. However, potentially lethal lacerations of internal organs can occur, because the net energy transfer to any given location may be substantial.

In blunt trauma, particular constellations of injury or injury patterns are associated with specific injury mechanisms. For example, when an unrestrained driver sustains a frontal impact, the head strikes the windshield, the chest and upper abdomen hit the steering column, and the legs or knees contact the dashboard. The resultant injuries can include facial fractures, cervical spine fractures, laceration of the thoracic aorta, myocardial contusion, injury to the spleen and liver, and fractures of the pelvis and lower extremities. When such patients are evaluated, the discovery of one of these injuries should prompt a search for the others. Collisions with side impact also carry the risk of cervical spine and thoracic trauma, diaphragm rupture, and crush injuries of the pelvic ring, but solid organ injury usually is limited to either the liver or spleen based on the direction of impact. Not surprisingly, any time a patient is ejected from the vehicle or thrown a significant distance from a motorcycle, the risk of any injury exists.

Penetrating injuries are classified according to the wound-ing agent (i.e., stab wound, gunshot wound, or shotgun wound). Gunshot wounds are subdivided further into high- and low-velocity injuries, because the speed of the bullet is much more important than its weight in determining kinetic energy. High-velocity gunshot wounds (bullet speed >2000 ft/s) are infrequent in the civilian setting. Shotgun injuries are divided into close-range (<20 feet) and long-range wounds. Close-range shotgun wounds are tantamount to high-velocity wounds because the entire energy of the load is delivered to a small area, often with devastating results. In contrast, long-range shotgun blasts result in a diffuse pellet pattern in which many pellets miss the victim, and those that do strike are dispersed and of comparatively low energy.

Regional Assessment and Special Diagnostic Tests

Based on mechanism, location of injuries identified on physical examination, screening radiographs, and the patient's overall condition, additional diagnostic studies often are indicated. However, the seriously injured patient is in constant jeopardy when undergoing special diagnostic testing; therefore, the surgeon must be in attendance and must be prepared to alter plans as circumstances demand. Hemodynamic, respiratory, and mental status will determine the most appropriate course of action. With these issues in mind, additional diagnostic tests are discussed on an anatomic basis.

Head Evaluation of the head includes examination for injuries to the scalp, eyes, ears, nose, mouth, facial bones, and intracranial

structures. Palpation of the head will identify scalp lacerations, which should be evaluated for depth, and depressed or open skull fractures. The eye examination includes not only pupillary size and reactivity, but also examination for visual acuity and for hemorrhage within the globe. Ocular entrapment, caused by orbital fractures with impingement on the ocular muscles, is evident when the patient cannot move his or her eyes through the entire range of motion. It is important to perform the eye examination early, because significant orbital swelling may prevent later evaluation. A lateral canthotomy may be needed to relieve periorbital pressure. The tympanic membrane is examined to identify hemotympanum, otorrhea, or rupture, which may signal an underlying head injury. Otorrhea, rhinorrhea, raccoon eyes, and Battle's sign (ecchymosis behind the ear) suggest a basilar skull fracture. Although such fractures may not require treatment, there is an association with blunt cerebrovascular injuries, cranial nerve injuries, and risk of meningitis.

Anterior facial structures should be examined to rule out fractures. This entails palpating for bony step-off of the facial bones and instability of the midface (by grasping the upper palate and seeing if this moves separately from the patient's head). A good question to ask awake patients is whether their bite feels normal to them; abnormal dental closure suggests malalignment of facial bones and a possibility for a mandible or maxillary fracture. Nasal fractures, which may be evident on direct inspection or palpation, typically bleed vigorously. This may result in the patient's having airway compromise due to blood running down the posterior pharynx, or there may be vomiting provoked by swallowed blood. Nasal packing or balloon tamponade may be necessary to control bleeding. Examination of the oral cavity includes inspection for open fractures, loose or fractured teeth, and sublingual hematomas.

All patients with a significant closed head injury (GCS score <14) should undergo CT scanning of the head. Additionally, elderly patients or those patients on antiplatelet agents or anticoagulation should be imaged despite a GCS of 15.^{31,32} For penetrating injuries, plain skull films may be helpful in the trauma bay to determine the trajectory of injury in hemodynamically unstable patients who cannot be transported for CT scan. The presence of lateralizing findings (e.g., a unilateral dilated pupil unresponsive to light, asymmetric movement of the extremities either spontaneously or in response to noxious stimuli, or unilateral Babinski's reflex) suggests an intracranial mass lesion or major structural damage.

Such lesions include hematomas, contusions, hemorrhage into ventricular and subarachnoid spaces, and diffuse axonal injury (DAI). Epidural hematomas occur when blood accumulates between the skull and dura, and are caused by disruption of the middle meningeal artery or other small arteries in that potential space, typically after a skull fracture (Fig. 7-16). Subdural hematomas occur between the dura and cortex and are caused by venous disruption or laceration of the parenchyma of the brain. Due to associated parenchymal injury, subdural hematomas have a much worse prognosis than epidural collections. Hemorrhage into the subarachnoid space may cause vasospasm and further reduce cerebral blood flow. Intraparenchymal hematomas and contusions can occur anywhere within the brain. DAI results from high-speed deceleration injury and represents direct axonal damage from shear effects. CT scan may demonstrate blurring of the gray and white matter interface and multiple small punctate hemorrhages, but magnetic resonance imaging is a more accurate test. Although prognosis for these injuries



Figure 7-16. Epidural hematomas (A) have a distinctive convex shape on computed tomographic scan, whereas subdural hematomas (B) are concave along the surface of the brain.

is extremely variable, early evidence of DAI is associated with a poor outcome. Stroke syndromes should prompt a search for carotid or vertebral artery injury using multislice CT angiography (CTA) (Fig. 7-17).

Significant intracranial penetrating injuries usually are produced by bullets from handguns, but an array of other weapons or instruments can injure the cerebrum via the orbit or through the thinner temporal region of the skull. Although the diagnosis usually is obvious, in some instances wounds in the auditory canal, mouth, and nose can be elusive. Prognosis is variable, but virtually all supratentorial wounds that injure both hemispheres are fatal.

Neck All blunt trauma patients should be assumed to have cervical spine injuries until proven otherwise. During cervical examination one must maintain cervical spine precautions

and in-line stabilization. Due to the devastating consequences of quadriplegia, a diligent evaluation for occult cervical spine injuries is mandatory. In the awake patient, the presence of posterior midline pain or tenderness should provoke a thorough radiologic evaluation. Additionally, intubated patients, patients with distracting injuries, or another identified spine fracture should undergo CT imaging. A ligamentous injury may not be visible with standard imaging techniques.³³ Flexion and extension views or MRI are obtained to further evaluate patients at risk or those with persistent symptoms, but generally are not done in the acute setting.

Spinal cord injuries can vary in severity. Complete injuries cause either quadriplegia or paraplegia, depending on the level of injury. These patients have a complete loss of motor function and sensation two or more levels below the bony injury.

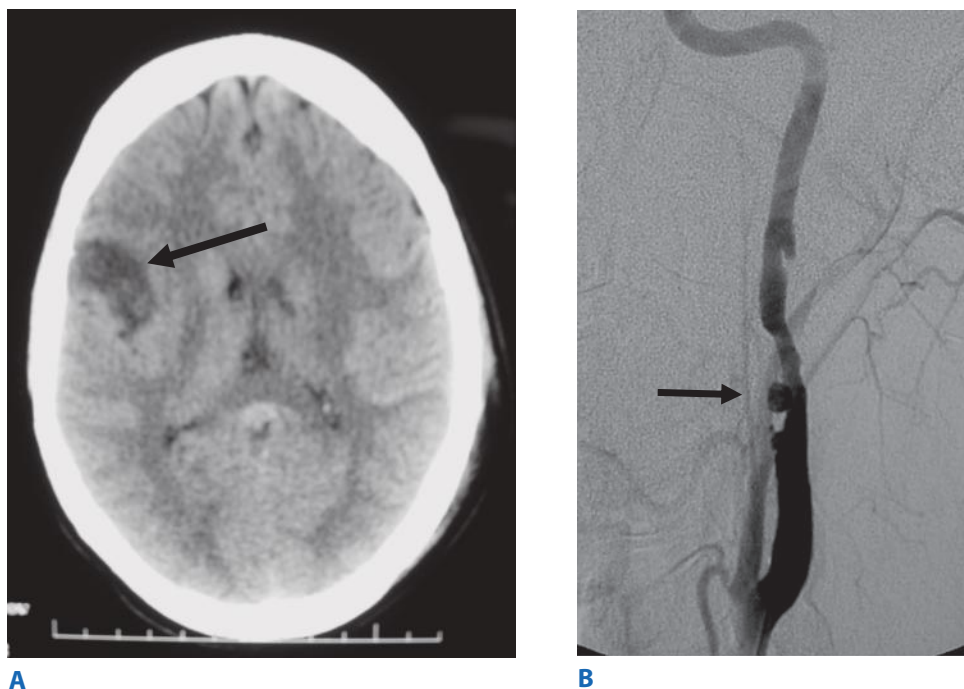


Figure 7-17. A. A right middle cerebral infarct noted on a computed tomographic scan of the head. Such a finding should prompt imaging to rule out an associated extracranial cerebrovascular injury. B. An internal carotid artery pseudoaneurysm documented by angiography.

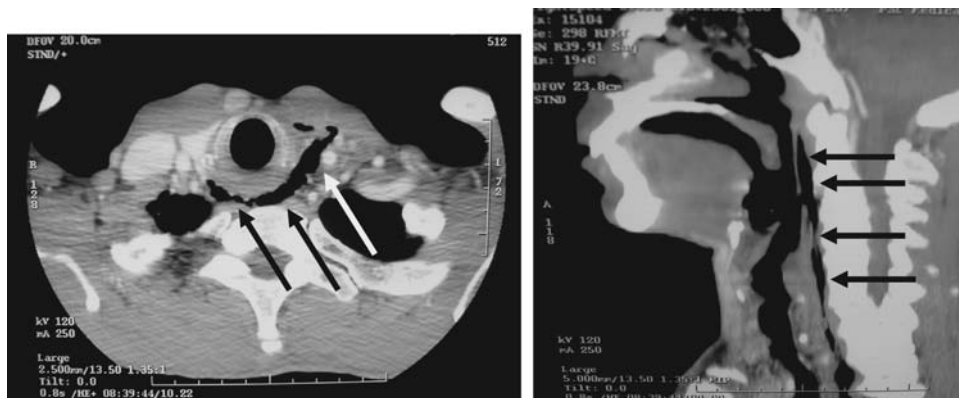


Figure 7-18. A laryngeal fracture results in air tracking around the trachea along the prevertebral space (arrows).

Patients with high spinal cord disruption are at risk for shock due to physiologic disruption of sympathetic fibers. Significant neurologic recovery is rare. However, there are several partial or incomplete spinal cord injury syndromes where the prognosis is better. Central cord syndrome typically occurs in older persons who experience hyperextension injuries. Motor function, pain, and temperature sensation are preserved in the lower extremities but diminished in the upper extremities. Some functional recovery usually occurs, but is often not a return to normal. Anterior cord syndrome is characterized by diminished motor function, pain, and temperature sensation below the level of the injury, but position sensing, vibratory sensation, and crude touch are maintained. Prognosis for recovery is poor. Brown-Séquard syndrome is usually the result of a penetrating injury in which one-half of the spinal cord is transected. This lesion is characterized by the ipsilateral loss of motor function, proprioception,

and vibratory sensation, whereas pain and temperature sensation are lost on the contralateral side.

During the primary survey, identification of injuries to the neck with exsanguination, expanding hematomas, airway obstruction, or aerodigestive injuries is a priority. A more subtle injury that may not be identified is a fracture of the larynx due to blunt trauma. Signs and symptoms include hoarseness, subcutaneous emphysema (Fig. 7-18), and a palpable fracture. Penetrating injuries of the anterior neck that violate the platysma are potentially life-threatening because of the density of critical structures in this region. Although operative exploration is appropriate in some circumstances, selective nonoperative management has been proven safe (Fig. 7-19).³⁴ Indications for immediate operative intervention for penetrating cervical injury include hemodynamic instability, significant external hemorrhage, or evidence of aerodigestive injury. The management

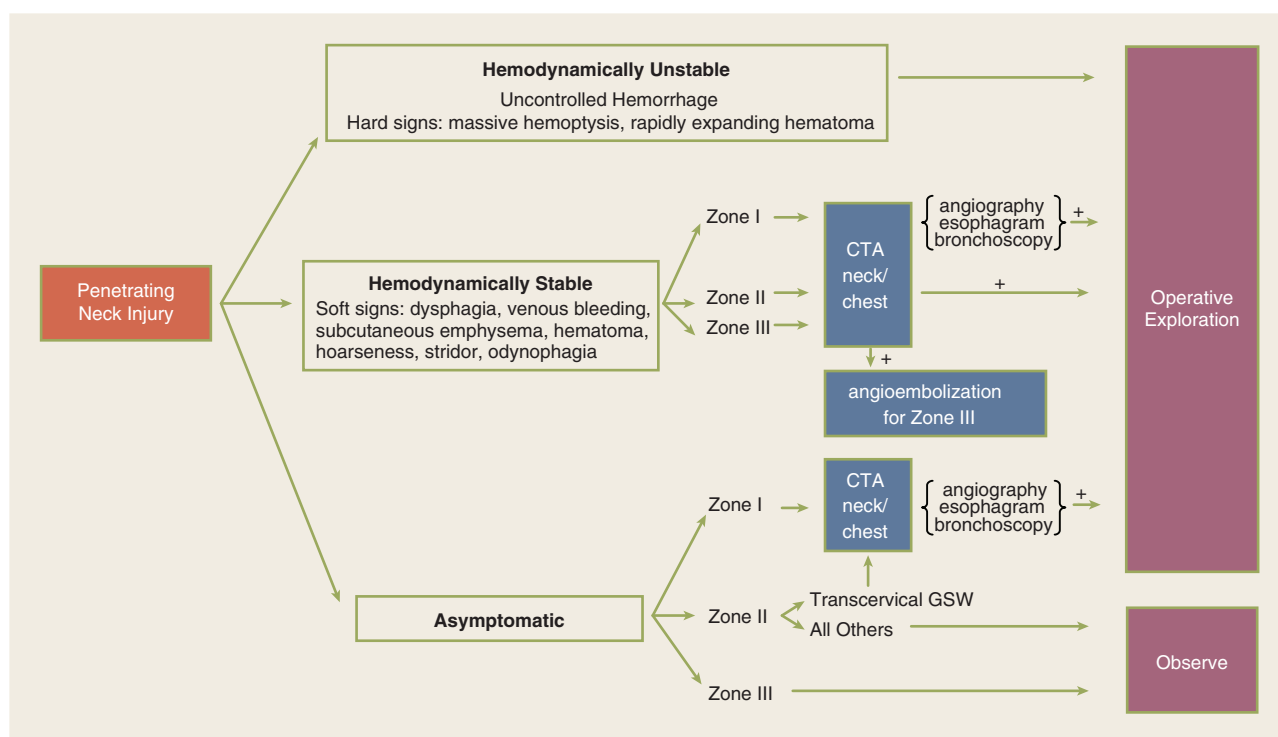


Figure 7-19. Algorithm for the management of penetrating neck injuries. CT = computed tomography; CTA = computed tomographic angiography; GSW = gunshot wound.

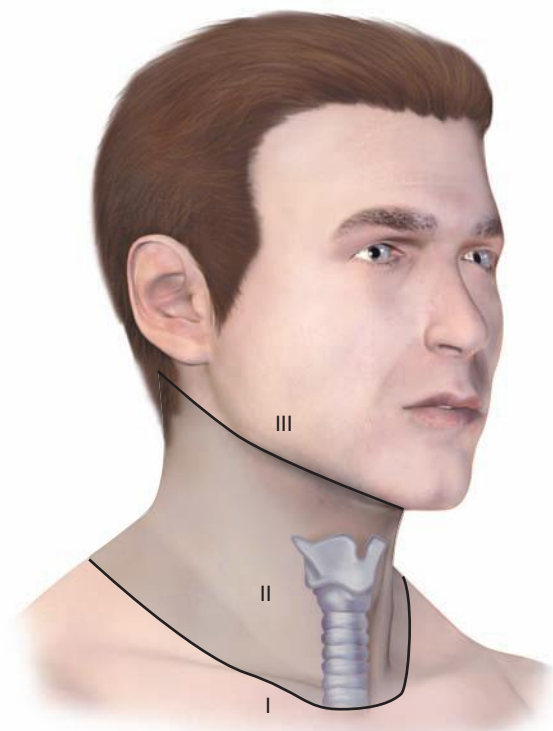


Figure 7-20. For the purpose of evaluating penetrating injuries, the neck is divided into three zones. Zone I is to the level of the clavicular heads and is also known as the *thoracic outlet*. Zone II is located between the clavicles and the angle of the mandible. Zone III is above the angle of the mandible.

algorithm for hemodynamically stable patients is based on the presenting symptoms and anatomic location of injury, with the neck being divided into three distinct zones (Fig. 7-20).

5► Zone I is inferior to the clavicles encompassing the thoracic outlet structures, zone II is between the thoracic outlet and the angle of the mandible, and zone III is above the angle of the mandible. Due to technical difficulties of injury exposure and varying operative approaches, a precise preoperative diagnosis is desirable for symptomatic zone I and III injuries. Therefore, these patients should ideally undergo diagnostic imaging before operation if they remain hemodynamically stable. Management of patients is further divided into those who are symptomatic and those who are not (Fig. 7-19). Specific symptoms or signs that should be identified include dysphagia, hoarseness, hematoma, venous bleeding, minor hemoptysis, and subcutaneous emphysema. Symptomatic patients should undergo CTA with further evaluation or operation based upon the imaging findings; less than 15% of penetrating cervical trauma requires neck exploration.³⁵ Asymptomatic patients are typically observed for 6 to 12 hours. The one caveat is asymptomatic patients with a transcervical gunshot wound; these patients should undergo CTA to determine the track of the bullet. CTA of the neck and chest determines trajectory of the injury tract; further studies are performed based on proximity to major structures.³⁵ Such additional imaging includes angiography, soluble contrast esophagram followed by barium esophagram, esophagoscopy, or bronchoscopy. Angiographic diagnosis, particularly of zone III injuries, can then be managed by selective angioembolization.

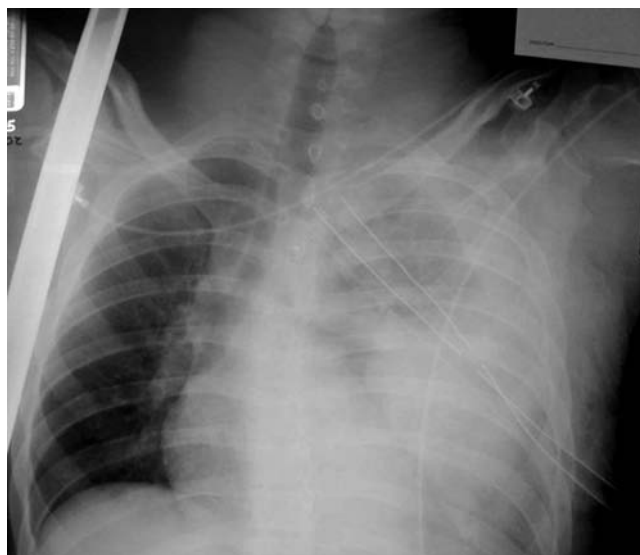


Figure 7-21. Persistence of a hemothorax despite two tube thoracostomies is termed a *caked hemothorax* and is an indication for prompt thoracotomy.

Chest Blunt trauma to the chest may involve the chest wall, thoracic spine, heart, lungs, thoracic aorta and great vessels, and rarely the esophagus. Most of these injuries can be evaluated by physical examination and chest radiography, with supplemental CT scanning based on initial findings. Any patient who undergoes an intervention in the ED—endotracheal intubation, central line placement, tube thoracostomy—needs a repeat chest radiograph to document the adequacy of the procedure. This is particularly true in patients undergoing tube thoracostomy for a pneumothorax or hemothorax. Patients with persistent pneumothorax, large air leaks after tube thoracostomy, or difficulty ventilating should undergo fiber-optic bronchoscopy to exclude a tracheobronchial injury or presence of a foreign body. Patients with hemothorax must have a chest radiograph documenting complete evacuation of the chest; a persistent hemothorax that is not drained by two chest tubes is termed a *caked hemothorax* and mandates immediate thoracotomy (Fig. 7-21).

Occult thoracic vascular injury must be diligently sought due to the high mortality of a missed lesion. Widening of the mediastinum on initial anteroposterior chest radiograph, caused by a hematoma around an injured vessel that is contained by the mediastinal pleura, suggests an injury of the great vessels. The mediastinal abnormality may suggest the location of the arterial injury (i.e., left-sided hematomas are associated with descending torn aortas, whereas right-sided hematomas are commonly seen with innominate injuries) (Fig. 7-22). Posterior rib fractures, sternal fractures with laceration of small vessels, and mediastinal venous bleeding also can produce similar hematomas. Other chest radiographic findings suggestive of an aortic tear are summarized in Table 7-5 (Fig. 7-23). However, at least 7% of patients with a descending torn aorta have a normal chest radiograph.³⁶ Therefore, screening spiral CT

6► scanning is performed based on the mechanism of injury: high-energy deceleration motor vehicle collision with frontal or lateral impact (> 30 mph frontal impact and >23 mph lateral impact), motor vehicle collision with ejection, falls of >25 ft, or direct impact (horse kick to chest, snowmobile or ski collision

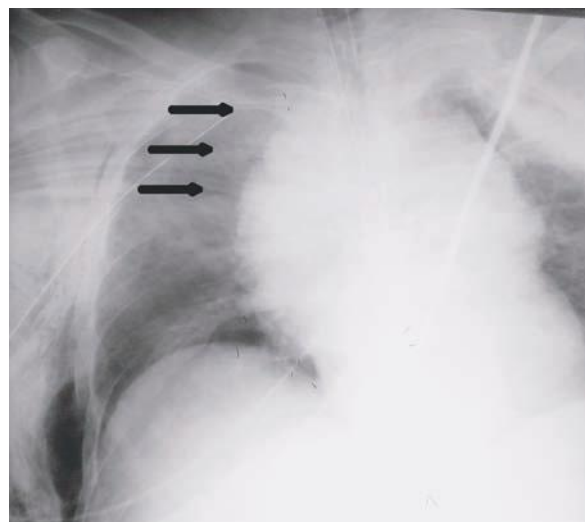
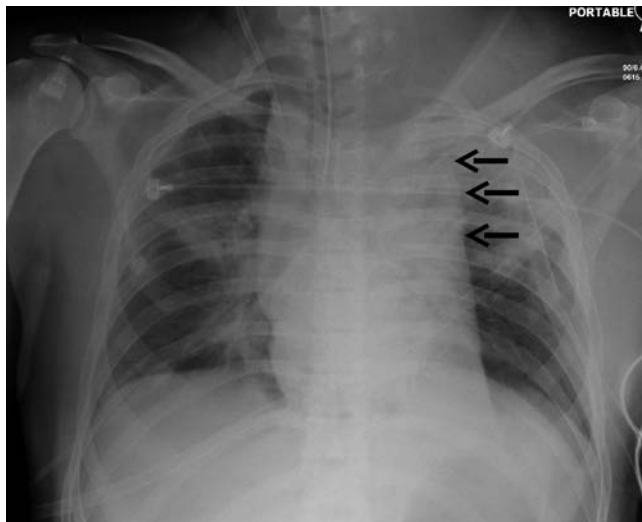
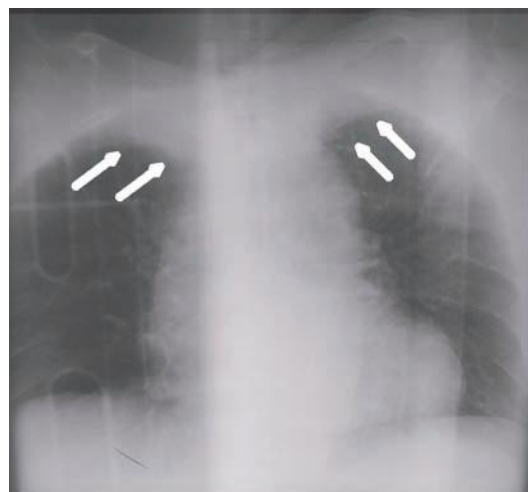


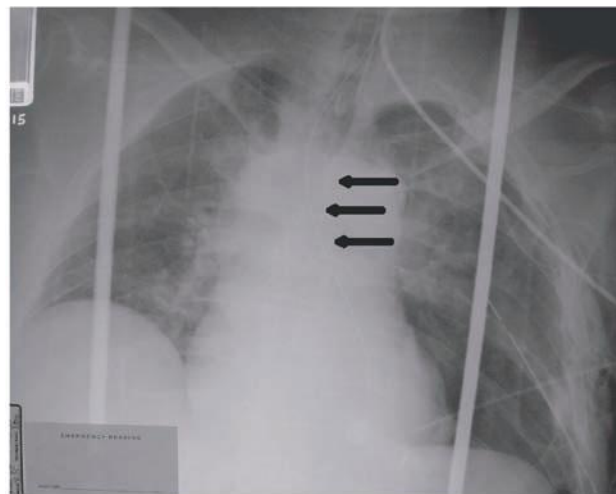
Figure 7-22. Location of the hematoma within the mediastinal silhouette suggests the type of great vessel injury. A predominant hematoma on the left suggests the far more common descending torn aorta (**A**; arrows), whereas a hematoma on the right indicates a relatively unusual but life-threatening innominate artery injury (**B**; arrows).

with tree).^{37,38} In >95% of patients who survive to reach the ED, the aortic injury occurs just distal to the left subclavian artery, where it is tethered by the ligamentum arteriosum (Fig. 7-24). In 2% to 5% of patients the injury occurs in the ascending aorta, in the transverse arch, or at the diaphragm. Reconstructions with multislice CTA obviate the need for invasive arteriography.³⁷

For penetrating thoracic trauma, physical examination, plain posteroanterior and lateral chest radiographs with metallic markings of wounds, pericardial ultrasound, and CVP measurement will identify the majority of injuries. Injuries of the esophagus and trachea are exceptions. Bronchoscopy should be performed to evaluate the trachea in patients with a persistent air leak from the chest tube or mediastinal air. Because esophagoscopy can miss injuries following an apparent normal endoscopy, patients at risk should undergo soluble contrast esophagography followed by barium examination to look for extravasation of contrast to identify an injury.³⁹ As with neck injuries, hemodynamically stable patients with transmediastinal gunshot wounds should undergo CT scanning to determine the path of the bullet; this identifies the vascular or visceral structures at risk for injury



A



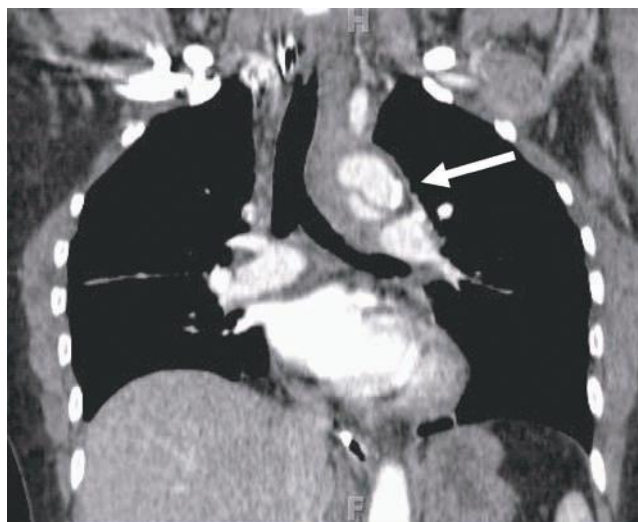
B

Table 7-5

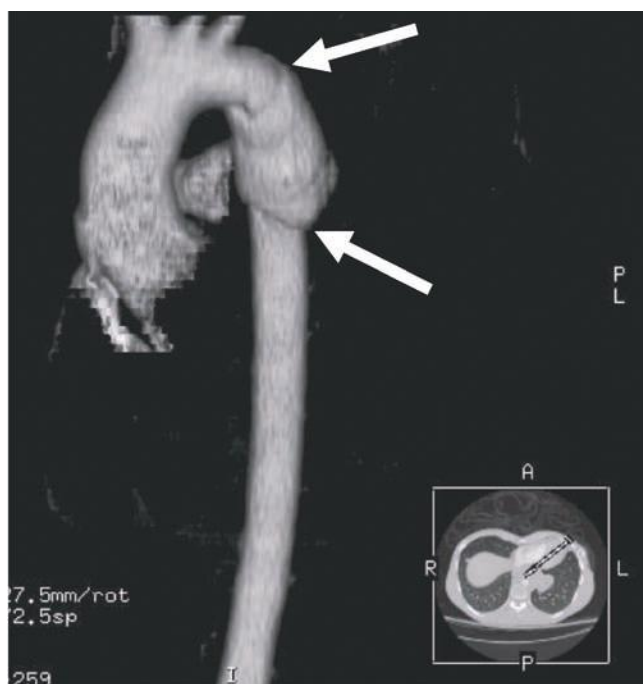
Findings on chest radiograph suggestive of a descending thoracic aortic tear

1. Widened mediastinum
2. Abnormal aortic contour
3. Tracheal shift
4. Nasogastric tube shift
5. Left apical cap
6. Left or right paraspinal stripe thickening
7. Depression of the left main bronchus
8. Obliteration of the aortopulmonary window
9. Left pulmonary hilar hematoma

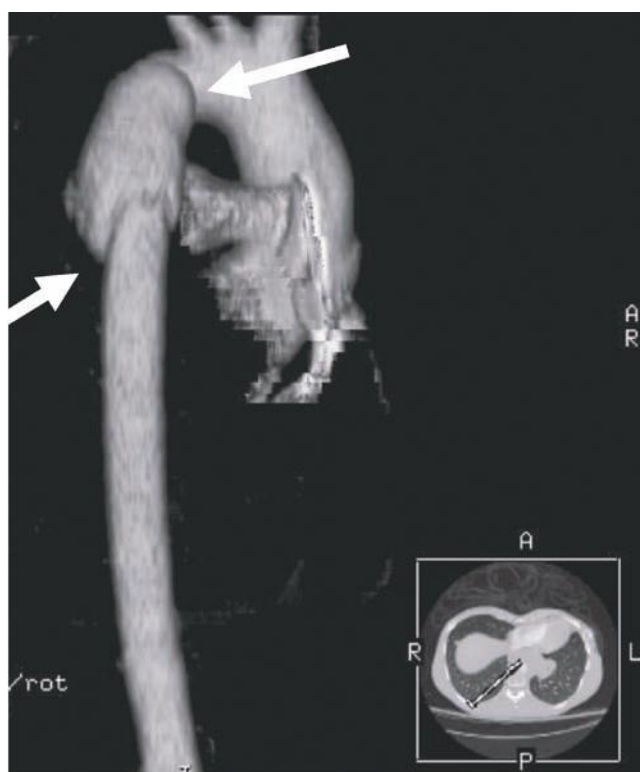
Figure 7-23. Chest film findings associated with descending torn aorta include apical capping (**A**; arrows) and tracheal shift (**B**; arrows).



A



B



C

Figure 7-24. Imaging to diagnose descending torn aorta includes computed tomographic angiography (A), with three-dimensional reconstructions (B, anterior; C, posterior) demonstrating the proximal and distal extent of the injury (arrows).

and directs angiography or endoscopy as appropriate. If there is a suspicion of a subclavian artery injury, brachial-brachial indices should be measured, but >60% of patients with an injury may not have a pulse deficit.⁴⁰ Therefore, CTA should be performed based on injury proximity to intrathoracic vasculature. Finally, with wounds identified on the chest, penetrating trauma should not be presumed to be isolated to the thorax. Injury to contiguous body cavities (i.e., the abdomen and neck) must be excluded; plain radiographs are a rapid, effective screening modality.

Abdomen The abdomen is a diagnostic black box. Fortunately, with few exceptions, it is not necessary to determine in the

7► emergency department which intra-abdominal organs are injured, only whether an exploratory laparotomy is necessary. However, physical examination of the abdomen can be unreliable in making this determination, and drugs, alcohol, and head and spinal cord injuries complicate clinical evaluation. The presence of abdominal rigidity and hemodynamic compromise is an undisputed indication for prompt surgical exploration. For the remainder of patients, a variety of diagnostic adjuncts are used to identify abdominal injury.

The diagnostic approach differs for penetrating trauma and blunt abdominal trauma. As a rule, minimal evaluation is

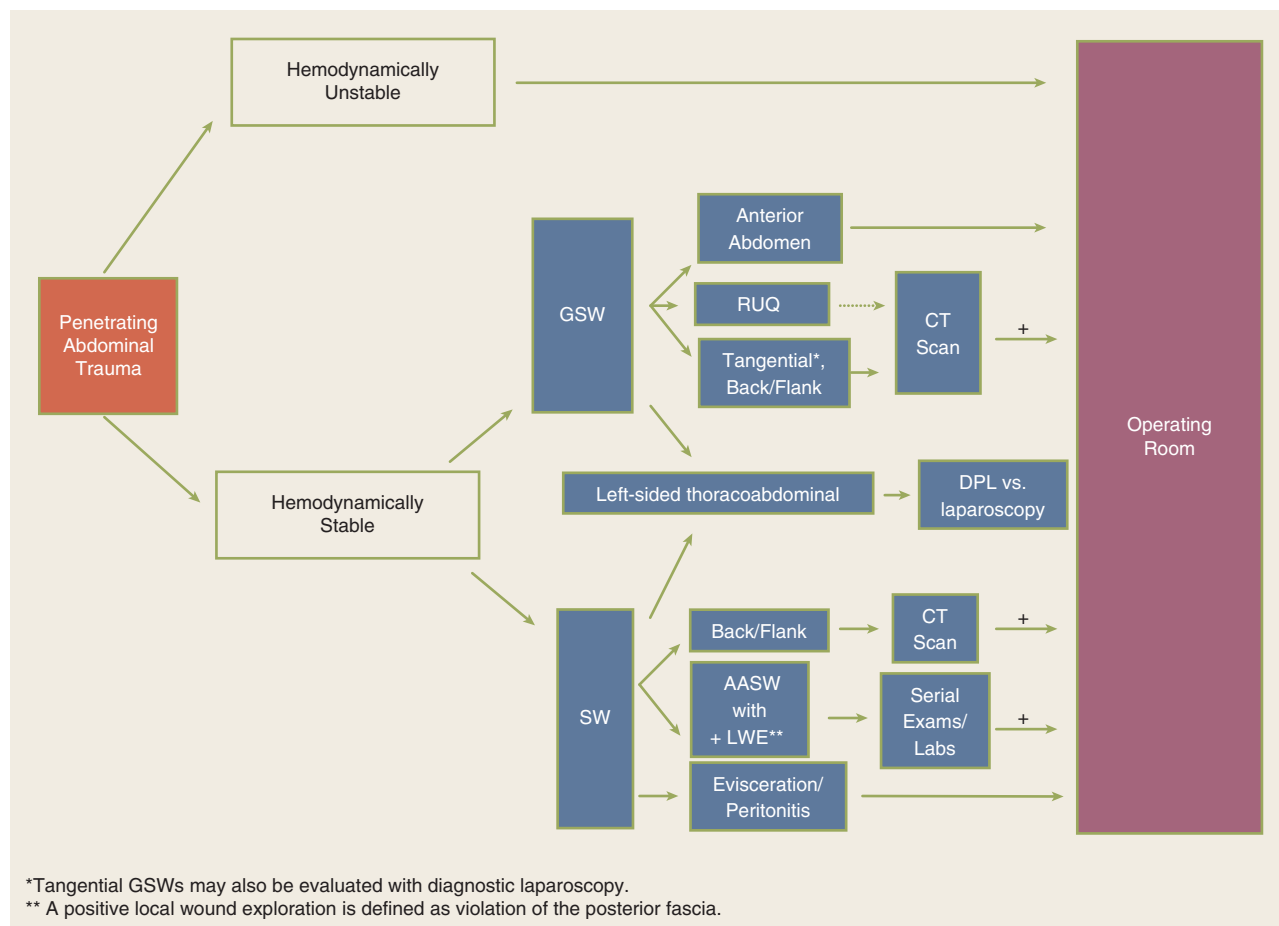


Figure 7-25. Algorithm for the evaluation of penetrating abdominal injuries. AASW = anterior abdominal stab wound; CT = computed tomography; DPL = diagnostic peritoneal lavage; GSW = gunshot wound; LWE = local wound exploration; RUQ = right upper quadrant; SW = stab wound.

required before laparotomy for gunshot or shotgun wounds that penetrate the peritoneal cavity, because over 90% of patients have significant internal injuries. Anterior truncal gunshot wounds between the fourth intercostal space and the pubic symphysis whose trajectory as determined by radiograph or wound location indicates peritoneal penetration should undergo laparotomy (Fig. 7-25). The exception is penetrating trauma isolated to the right upper quadrant; in hemodynamically stable patients with trajectory confined to the liver by CT scan, nonoperative observation may be reasonable.⁴¹ In obese patients, if the gunshot wound is thought to be tangential through the subcutaneous tissues, CT scan can delineate the track and exclude peritoneal violation. Laparoscopy is another option to assess peritoneal penetration for tangential wounds. If there is doubt, however, it is always safer to explore the abdomen. In the scenario of tangential high energy GSWs, however, it is possible to sustain a transmitted intraperitoneal hollow visceral injury due to a blast insult. Gunshot wounds to the back or flank are more difficult to evaluate because of the retroperitoneal location of the injured abdominal organs. Triple-contrast CT scan can delineate the trajectory of the bullet and identify peritoneal violation or retroperitoneal entry, but may not identify the specific injuries. In contrast to gunshot wounds, stab wounds that penetrate the peritoneal cavity are less likely to injure intra-abdominal organs. Anterior abdominal stab wounds (from costal margin to inguinal

ligament and bilateral midaxillary lines) should be explored under local anesthesia in the ED to determine if the fascia has been violated. Injuries that do not penetrate the peritoneal cavity do not require further evaluation, and the patient may be discharged from the ED. Patients with fascial penetration must be further evaluated for intra-abdominal injury, because there is up to a 50% chance of requiring laparotomy. Debate remains over whether the optimal diagnostic approach is serial examination, diagnostic peritoneal lavage (DPL), or CT scanning; the most recent evidence supports serial examination and laboratory evaluation.^{42,43} Patients with stab wounds to the right upper quadrant can undergo CT scanning to determine trajectory and confinement to the liver for potential nonoperative care.⁴¹ Those with stab wounds to the flank and back should undergo triple-contrast CT to assess for the potential risk of retroperitoneal injuries of the colon, duodenum, and urinary tract.

Penetrating thoracoabdominal wounds may cause occult injury to the diaphragm. Patients with gunshot or stab wounds to the left lower chest should be evaluated with diagnostic laparoscopy or DPL to exclude diaphragmatic injury. For patients undergoing DPL evaluation, laboratory value cutoffs to rule out diaphragm injury are different from traditional values formerly used for abdominal stab wounds (see Table 7-6). An RBC count of >10,000/ μ L is considered a positive finding and an indication for abdominal evaluation; patients with a DPL RBC count

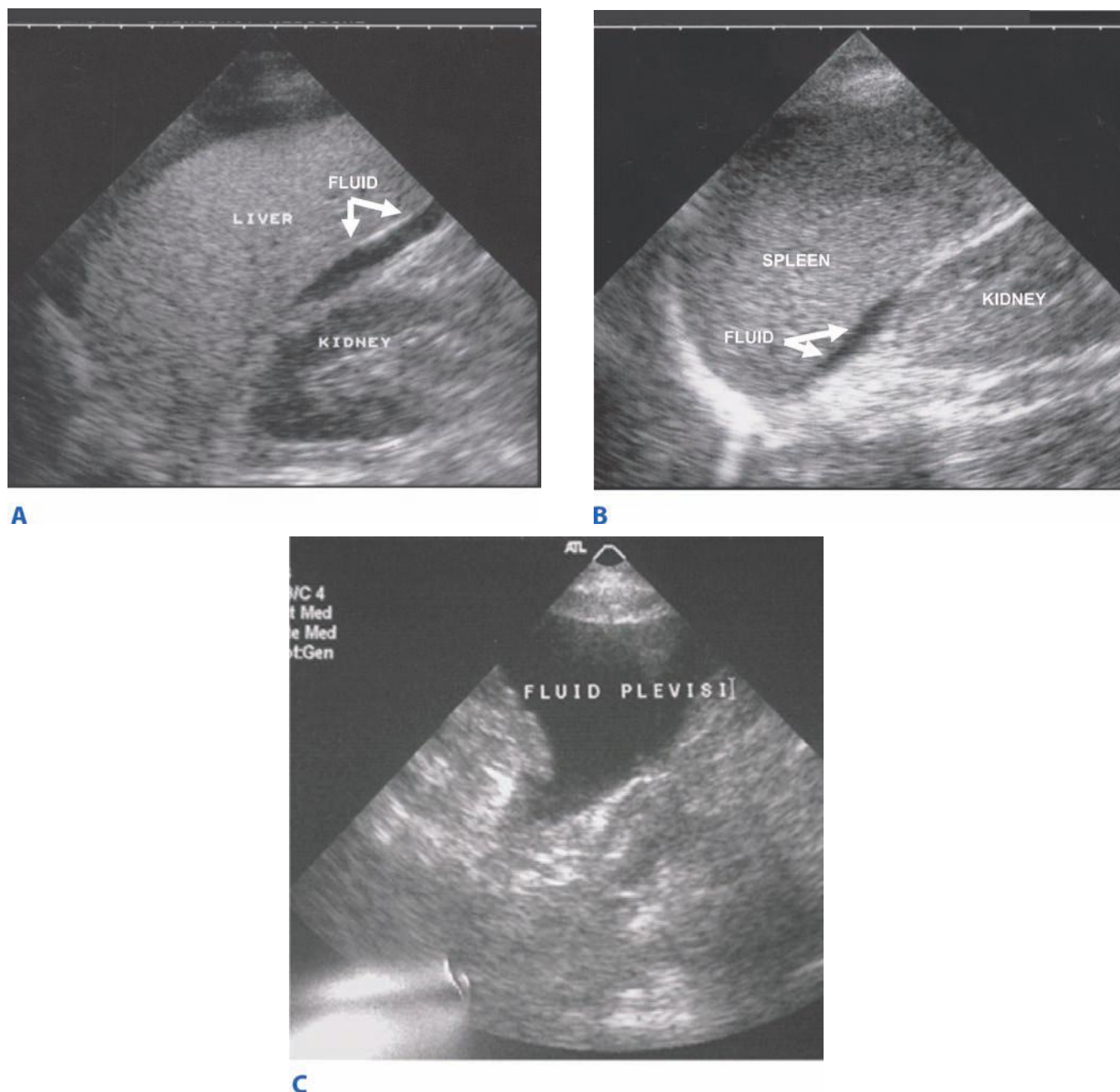


Figure 7-27. Focused abdominal sonography for trauma imaging detects intra-abdominal hemorrhage. Hemorrhage is presumed when a fluid stripe is visible between the right kidney and liver (**A**), between the left kidney and spleen (**B**), or in the pelvis (**C**).

indications for operative exploration, whereas soft signs are indications for further testing or observation. Bony fractures or knee dislocations should be realigned before definitive vascular examination. On-table angiography may be useful to localize the arterial injury and thus, limit tissue dissection in patients with hard signs of vascular injury. For example, a patient with an absent popliteal pulse and femoral shaft fracture due to a bullet that entered the lateral hip and exited below the medial knee could have injured either the femoral or popliteal artery anywhere along its course (Fig. 7-31). In management of vascular trauma, controversy exists regarding the treatment of patients with soft signs of injury, particularly those with injuries in proximity to major vessels. It is known that some of these patients will have arterial injuries that require repair. The most common

approach has been to measure SBP using Doppler ultrasonography and compare the value for the injured side with that for the uninjured side, termed the *A-A index*.⁴⁷ If the pressures are within 10% of each other, a significant injury is unlikely and no further evaluation is performed. If the difference is >10%, CT angiography or arteriography is indicated. Others argue that there are occult injuries, such as pseudoaneurysms or injuries of the profunda femoris or peroneal arteries, which may not be detected with this technique. If hemorrhage occurs from these injuries, compartment syndrome and limb loss may occur. Although busy trauma centers continue to debate this issue, the surgeon who is obliged to treat the occasional injured patient may be better served by performing CT angiography in selected patients with soft signs. Blunt or penetrating trauma to the

Table 7-7

American Association for the Surgery of Trauma grading scales for solid organ injuries

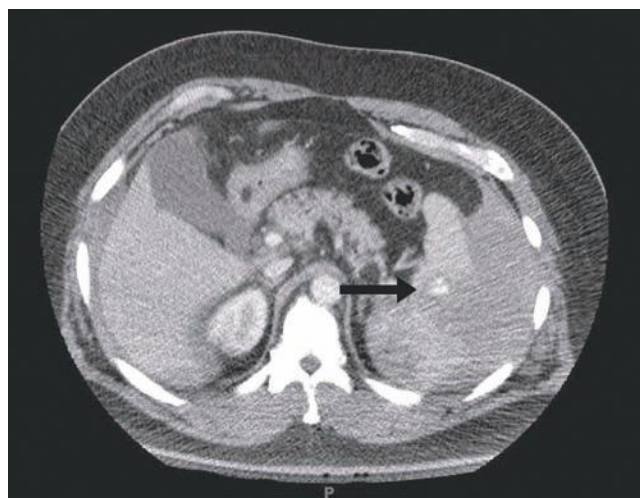
	SUBCAPSULAR HEMATOMA	LACERATION
Liver Injury Grade		
Grade I	<10% of surface area	<1 cm in depth
Grade II	10%–50% of surface area	1–3 cm
Grade III	>50% of surface area or >10 cm in depth	>3 cm
Grade IV	25%–75% of a hepatic lobe	
Grade V	>75% of a hepatic lobe	
Grade VI	Hepatic avulsion	
Splenic Injury Grade		
Grade I	<10% of surface area	<1 cm in depth
Grade II	10%–50% of surface area	1–3 cm
Grade III	>50% of surface area or >10 cm in depth	>3 cm
Grade IV	>25% devascularization	Hilum
Grade V	Shattered spleen Complete devascularization	

extremities requires an evaluation for fractures, ligamentous injury, and neurovascular injury. Plain radiographs are used to evaluate fractures, whereas ligamentous injuries, particularly those of the knee and shoulder, can be imaged with magnetic resonance imaging.

GENERAL PRINCIPLES OF MANAGEMENT

Over the past 25 years there has been a remarkable change in management practices and operative approach for the injured patient. With the advent of CT scanning, nonoperative management of solid organ injuries has replaced routine operative exploration. Those patients who do require operation may be treated with less radical resection techniques, such as splenorrhaphy or

partial nephrectomy. Colonic injuries, previously mandating colostomy, are now repaired primarily in virtually all cases. Additionally, the type of anastomosis has shifted from a double-layer closure to a continuous running single-layer closure; this method is technically equivalent to and faster than the interrupted multilayer techniques.⁴⁸ Adoption of damage control surgical techniques in physiologically deranged patients has resulted in limited initial operative time, with definitive injury repair delayed until after resuscitation in the surgical intensive care unit (SICU) with physiologic restoration.⁴⁹ Abdominal drains, once considered mandatory for parenchymal injuries and some anastomoses, have disappeared; fluid collections are managed by percutaneous techniques. Newer endovascular techniques such as stenting of arterial injuries and angioembolization are routine



A



B

Figure 7-28. Computed tomographic images reveal critical information about solid organ injuries, such as associated contrast extravasation from a grade IV laceration of the spleen (**A**; arrows) and the amount of subcapsular hematoma in a grade III liver laceration (**B**; arrows).

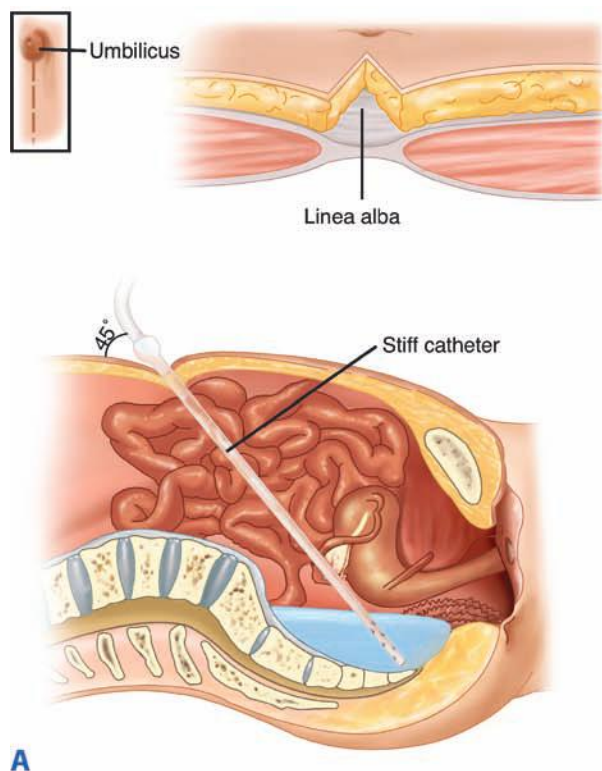
**A****B**

Figure 7-29. Diagnostic peritoneal lavage is performed through an infraumbilical incision unless the patient has a pelvic fracture or is pregnant. **A.** The linea alba is sharply incised, and the catheter is directed into the pelvis. **B.** The abdominal contents should initially be aspirated using a 10-mL syringe.

adjuncts. Blunt cerebrovascular injuries have been recognized as a significant, preventable source of neurologic morbidity and mortality. The use of preperitoneal pelvic packing for unstable pelvic fractures as well as early fracture immobilization with external fixators are paradigm shifts in management. Finally, the institution of massive transfusion protocols balances the benefit of blood component therapy against immunologic risk. Viscoelastic hemostatic assays (TEG and ROTEM) have been shown to be superior to traditional laboratory tests, and have been central to the evolving concept of goal-directed hemostasis.⁵⁰ These conceptual changes have significantly improved survival of critically injured patients; they have been promoted and critically reviewed by academic trauma centers via forums such as the American College of Surgeons Committee on Trauma, the American Association for the Surgery of Trauma, the International Association of Trauma Surgery and Intensive Care, the Pan-American Trauma Congress, and other surgical organizations.

Transfusion Practices

Injured patients with life-threatening hemorrhage develop an acute coagulopathy of trauma (ACOT). Cohen et al⁵¹ have shown convincingly that activated protein C is a key element, although the complete mechanism remains to be elucidated. Fibrinolysis is another important component of the ACOT; present in only 5% of injured patients requiring hospitalization, but 20% in those requiring massive transfusion.⁵² Fresh whole blood, arguably the optimal replacement, is not available in the United States. Rather, its component parts, packed red blood cells (PRBCs), fresh-frozen plasma, platelets, and cryoprecipitate, are administered. Specific transfusion triggers

for individual blood components exist. Although current critical care guidelines indicate that PRBC transfusion should occur once the patient's hemoglobin level is <7 g/dL,⁵³ in the acute phase of resuscitation a hemoglobin of 10 g/dL is suggested to facilitate hemostasis.⁵⁴ The traditional thresholds for blood component replacement in the patient manifesting a coagulopathy have been INR >1.5 , PTT >1.5 normal, platelet count $>50,000/\mu\text{L}$, and fibrinogen >100 mg/dl. However, these guidelines have been replaced by TEG and ROTEM criteria in many trauma centers. Such guidelines are designed to limit the transfusion of immunologically active blood components and decrease the risk of transfusion-associated lung injury and secondary multiple organ failure.^{55,56}

In the critically injured patient requiring large amounts of blood component therapy, a massive transfusion protocol should be followed (Fig. 7-32). This approach calls for administration of various components in a specific ratio during transfusion to achieve restoration of blood volume and correction of coagulopathy. Although the optimal ratio is yet to be determined, current scientific evidence indicates a presumptive 1:2 red cell:plasma ratio in patients at risk for massive transfusion (10 units of PRBCs in 6 hours).⁵⁷⁻⁶⁰ Because complete typing and cross-matching takes up to 45 minutes, patients requiring emergent transfusions are given type O, type-specific, or biologically compatible RBCs. Blood typing, and to a lesser extent cross-matching, is essential to avoid life-threatening intravascular hemolytic transfusion reactions. Trauma centers and their associated blood banks must have the capability of transfusing tremendous quantities of blood components, because it is not unusual to have 100 component units transfused during one procedure and have the patient survive. Massive transfusion

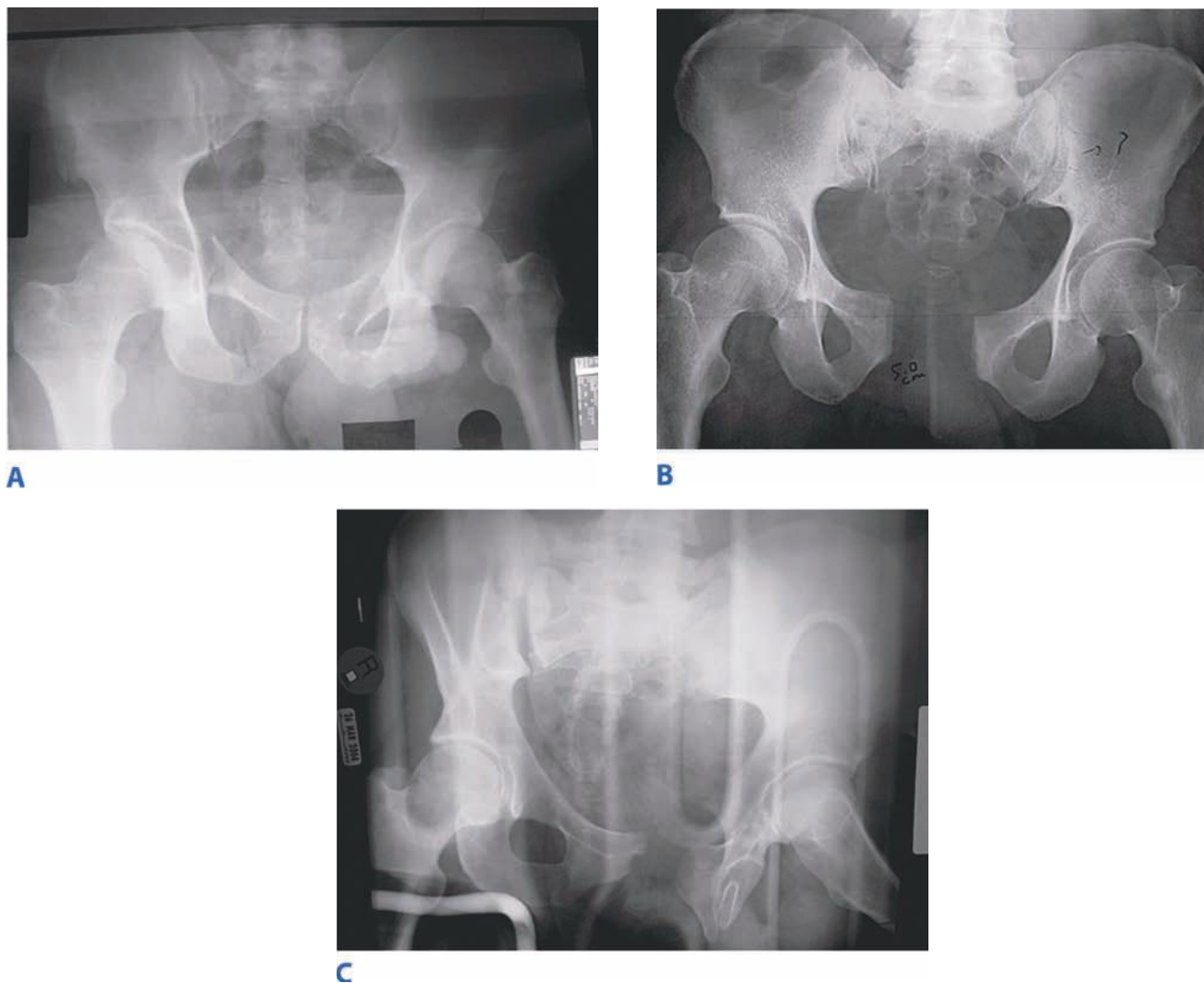


Figure 7-30. The three types of mechanically unstable pelvis fractures are lateral compression (A), anteroposterior compression (B), and vertical shear (C).

protocols, established preemptively, permit coordination of the activities of surgeons, anesthesiologists, and blood bank directors to facilitate transfusion at these rates should a crisis occur.

Postinjury coagulopathy is associated with core hypothermia and metabolic acidosis, termed the *bloody vicious cycle*.⁴⁹

8► The pathophysiology is multifactorial and includes

inhibition of temperature-dependent enzyme-activated coagulation cascades, platelet dysfunction, endothelial abnormalities, and fibrinolytic activity. Such coagulopathy may be insidious, so the surgeon must be cognizant of subtle signs such as excessive bleeding from the cut edges of skin. Although the coagulopathic “ooze” may seem minimal compared with the torrential hemorrhage from a hole in the aorta, blood loss from the entire area of dissection can lead to exsanguination. Point-of-care TEG results, which provide a comprehensive assessment of clot capacity and fibrinolysis, can be available within 10 minutes. This concept has been termed . In contrast, traditional laboratory tests of coagulation capability (i.e., INR, PTT, fibrinogen levels, and platelet count) requires at least 30 minutes. Such a delay is particularly troublesome for patients who have lost two blood volumes while waiting for the test results to return. Using damage control techniques to limit operative time and provide physiologic restoration in the SICU can be lifesaving (see section *Damage Control Surgery*).

Prophylactic Measures

All injured patients undergoing an operation should receive preoperative antibiotics. The type of antibiotic is determined

Table 7-8

Signs and symptoms of peripheral arterial injury

HARD SIGNS (OPERATION MANDATORY)	SOFT SIGNS (FURTHER EVALUATION INDICATED)
Pulsatile hemorrhage	Proximity to vasculature
Absent pulses	Significant hematoma
Acute ischemia	Associated nerve injury
	A-A index of <0.9
	Thrill or bruit

A-A index = systolic blood pressure on the injured side compared with that on the uninjured side.



Figure 7-31. On-table angiography in the operating room isolates the area of vascular injury to the superficial femoral artery in a patient with a femoral fracture after a gunshot wound to the lower extremity.

by the anticipated source of contamination in the abdomen or other operative region; additional doses should be administered during the procedure based on blood loss and the half-life of the antibiotic. Extended postoperative antibiotic therapy is administered only for contaminated open fractures. Tetanus prophylaxis is administered to all patients according to published guidelines.

Trauma patients are at risk for venous thromboembolism and its associated morbidity and mortality. In fact, pulmonary embolus can occur much earlier in the patient's hospital course than previously believed.⁶¹ Patients at higher risk for venous thromboembolism are those with multiple fractures of the pelvis and lower extremities, coma or spinal cord injury, and requiring ligation of large veins in the abdomen and lower extremities. Morbidly obese patients and those over 55 years of age are at additional risk. Administration of low molecular weight heparin (LMWH) is initiated as soon as bleeding has been controlled and there is stable intracranial pathology. Higher doses of LMWH are required in injured patients to attain adequate anti-Xa levels, and antiplatelet therapy should probably be added. In high-risk patients, removable inferior vena caval filters should be considered if there are prolonged contraindications to administration of LMWH. Additionally, pulsatile compression stockings (also termed *sequential compression devices*) are used routinely unless there is a fracture.

A final prophylactic measure that is usually not considered is thermal protection. Hemorrhagic shock impairs perfusion and metabolic activity throughout the body, with resultant decrease in heat production and body temperature. Removing the patient's clothes causes a second thermal insult, and infusion of cold PRBCs or room temperature crystalloid exacerbates the

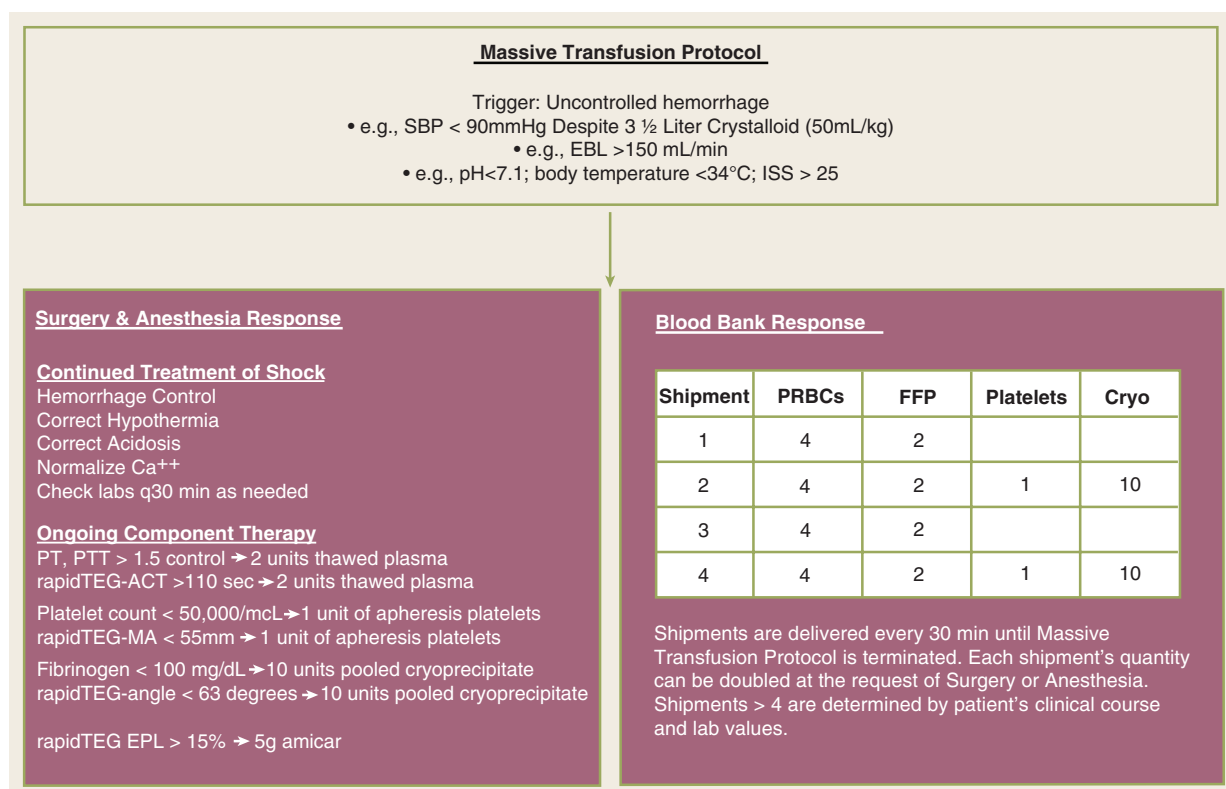


Figure 7-32. Denver Health Medical Center's Massive Transfusion Protocol. ACT = activated clotting time; Cryo = cryoprecipitate; FFP = fresh-frozen plasma; INR = International Normalized Ratio; MA = maximum amplitude; PRBCs = packed red blood cells; PTT = partial thromboplastin time; SBP = systolic blood pressure; TEG = thromboelastography; EPL = estimated percent lysis.

problem. As a result, injured patients can become hypothermic, with temperatures below 34°C (93.2°F) upon arrival in the OR. Hypothermia aggravates coagulopathy and provokes myocardial irritability. Therefore, prevention must begin in the ED by maintaining a comfortable ambient temperature, covering patients with warm blankets, and administering warmed IV fluids and blood products. Additionally, in the OR a Bair Hugger® warmer (the upper body or lower body blanket) and heated inhalation via the ventilatory circuit is instituted. For cases of severe hypothermia (temperature <30°C [86°F]), arteriovenous rewarming should be considered.

Operative Approaches and Exposure

Cervical Exposure Operative exposure for midline structures of the neck (e.g., trachea, thyroid, bilateral carotid sheaths) is

obtained through a collar incision; this is typically performed two finger breadths above the sternal notch, but can be varied based on the level of anticipated injury. After subplatysmal flap elevation, the strap muscles are divided in the midline to gain access to the central neck compartment. More superior and lateral structures are accessed by extending the collar incision upward along the sternocleidomastoid muscle; this may be done bilaterally if necessary. Unilateral neck exploration is done through an incision extending from the mastoid down to the clavicle, along the anterior border of the sternocleidomastoid muscle (Fig. 7-33). The carotid sheath, containing the carotid artery, jugular vein, and vagus nerve, is opened widely to examine these structures. The facial vein, which marks the carotid bifurcation, is usually ligated for exposure of the internal carotid artery.

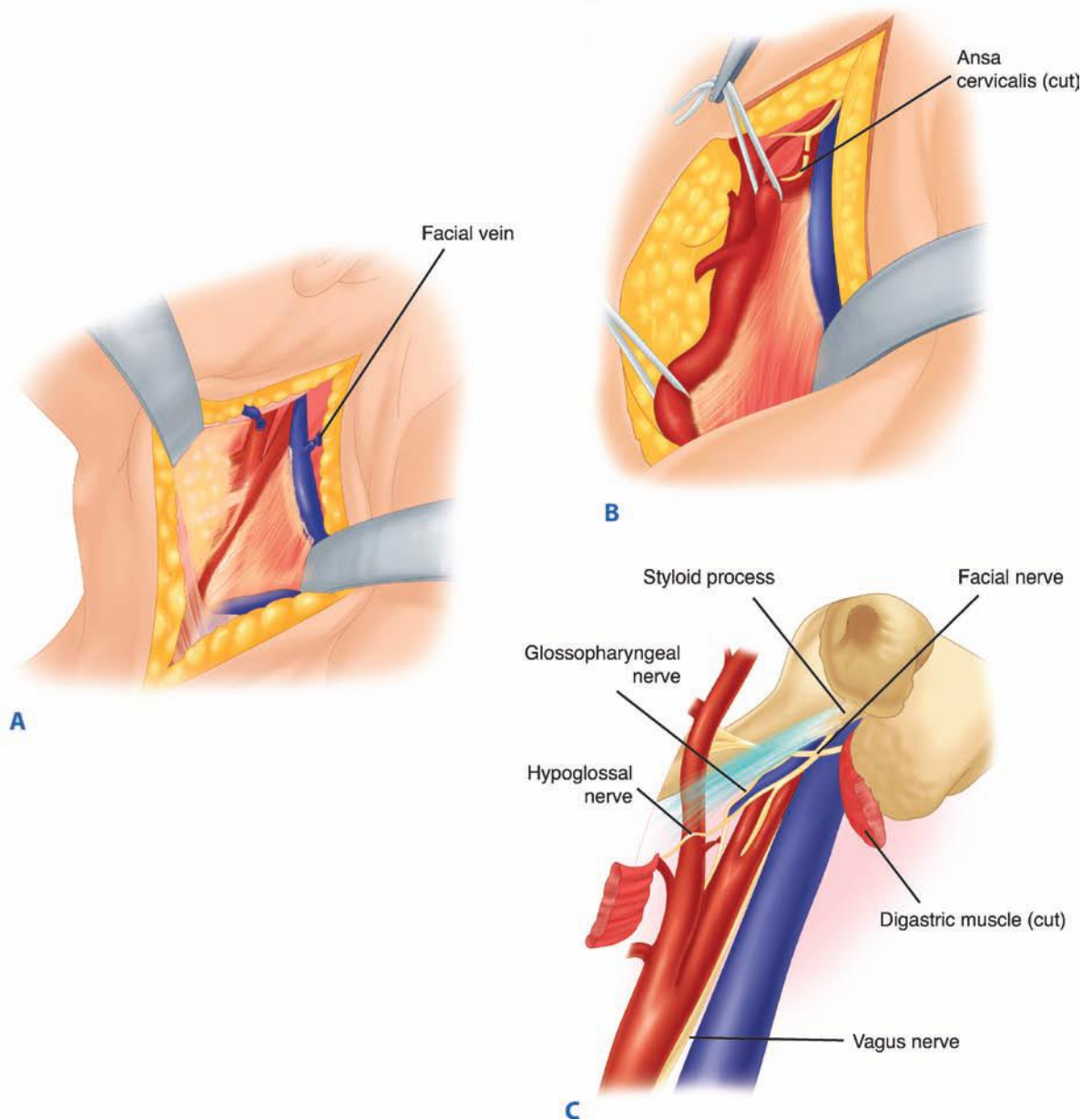


Figure 7-33. A. Unilateral neck exploration is performed through an incision along the anterior border of the sternocleidomastoid muscle; exposure of the carotid artery requires early division of the facial vein. B. The distal internal carotid artery is exposed by dividing the ansa cervicalis, which permits mobilization of the hypoglossal nerve. C. Further exposure is facilitated by resection of the posterior belly of the digastric muscle.

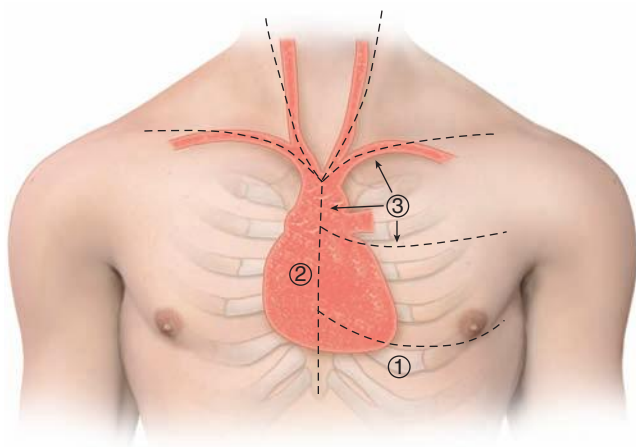
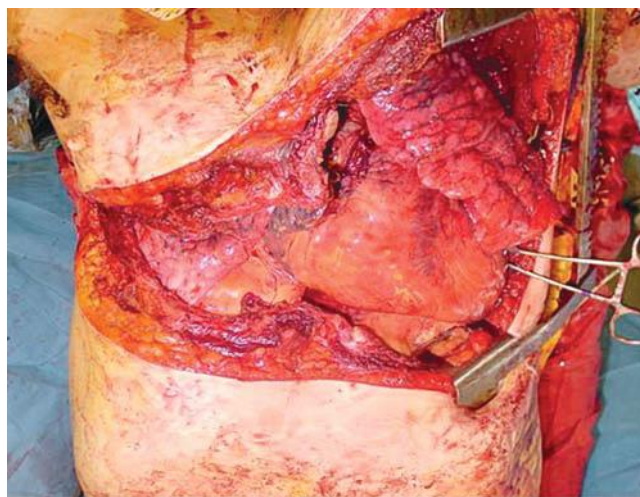


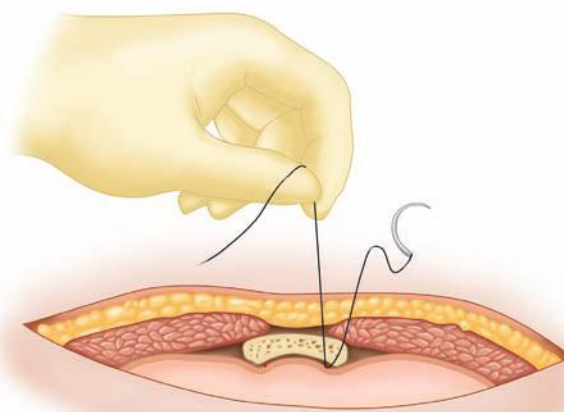
Figure 7-34. Options for thoracic exposure include the most versatile incision, the anterolateral thoracotomy (1), as well as a median sternotomy (2) and a “trap door” thoracotomy (3). Any thoracic incision may be extended into a supraclavicular or anterior neck incision for wider exposure.

Exposure of the distal carotid artery in zone III is difficult (see Fig. 7-33). The first step is division of the ansa cervicalis to facilitate mobilization of the hypoglossal nerve. Next, the posterior portion of the digastric muscle, which overlies the internal carotid, is transected. The glossopharyngeal and vagus nerves are also mobilized and retracted as necessary. If accessible, the styloid process and attached muscles are removed. At this point anterior displacement of the mandible (subluxation) may be helpful. In desperate situations, the vertical ramus of the mandible may be divided. However, this maneuver often entails resection of the parotid gland and the facial nerve is at risk for exposure of the distal internal carotid.

Thoracic Incisions An anterolateral thoracotomy, with the patient placed supine, is the most versatile incision for emergent thoracic exploration. The location of the incision is in the fifth interspace, in the inframammary line (Fig. 7-34). If access is needed to both pleural cavities, the original incision can be extended across the sternum with a Lebsche knife, into a “clamshell” thoracotomy (Fig. 7-35). If the sternum is divided, the internal mammary arteries should be ligated to prevent blood loss. The heart, lungs, descending aorta, pulmonary hilum, and esophagus are accessible with this approach. For control of the great vessels, the superior portion of the sternum may be divided with extension of the incision into the neck considered. A method advocated for access to the proximal left subclavian artery is through a fourth interspace anterolateral thoracotomy, superior sternal extension, and left supraclavicular incision (“trap door” thoracotomy). Although the trap door procedure is appropriate after resuscitative thoracotomy, the proximal left subclavian artery can be accessed more easily via a sternotomy with a supraclavicular extension. If the left subclavian artery is injured outside the thoracic outlet, vascular control can be obtained via the sternotomy and definitive repair done through the supraclavicular incision. Emergent median sternotomy is limited to anterior stab wounds to the heart. Typically, these patients have pericardial tamponade and undergo placement of a pericardial drain before a semiurgent median sternotomy is performed. Patients in extremis, however, should undergo anterolateral thoracotomy.



A



B

Figure 7-35. A. A “clamshell” thoracotomy provides exposure to bilateral thoracic cavities. B. Sternal transection requires individual ligation of both the proximal and distal internal mammary arteries on the undersurface of the sternum.

Median sternotomy with cervical extension is used for rapid exposure in patients with presumed proximal subclavian, innominate, or proximal carotid artery injuries. Care must be taken to avoid injury to the phrenic and vagus nerves that pass over the subclavian artery and to the recurrent laryngeal nerve passing posteriorly. Posterolateral thoracotomies are used for exposure of injuries to the trachea or main stem bronchi near the carina (right posterolateral thoracotomy), tears of the descending thoracic aorta (left posterolateral thoracotomy with left heart bypass), and intrathoracic esophageal injuries.

Emergent Abdominal Exploration Abdominal exploration in adults is performed using a generous midline incision because of its versatility. For children under the age of 6, a transverse incision may be advantageous. Making the incision is faster with a scalpel than with an electrosurgical unit; incisional abdominal wall bleeding should be ignored until intra-abdominal sources of hemorrhage are controlled. Liquid and clotted blood are evacuated with multiple laparotomy pads to identify the major source(s) of active bleeding. After blunt trauma the spleen and liver should be palpated first and packed if fractured, and

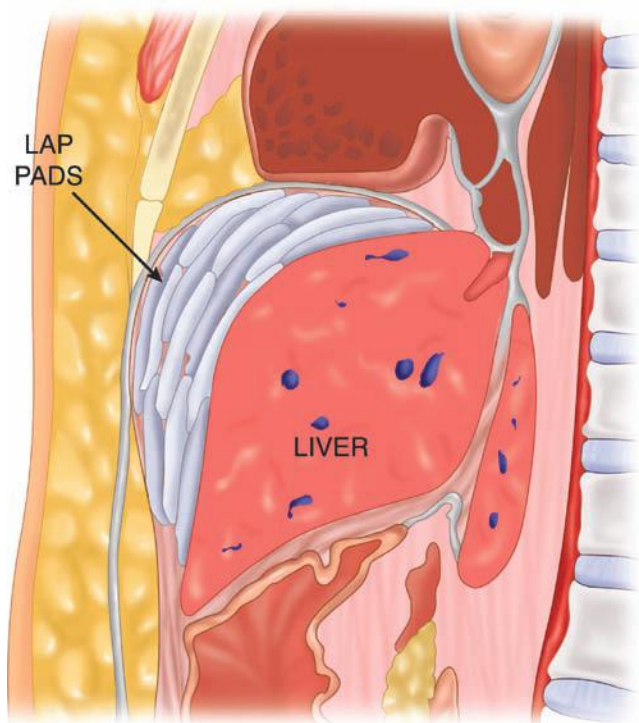


Figure 7-36. A sagittal view of packs placed to control hepatic hemorrhage. Lap = laparotomy.

the infracolic mesentery inspected to exclude a zone I vascular injury. In contrast, after a penetrating wound the search for bleeding should pursue the trajectory of the penetrating device. If the patient has an SBP of <70 mmHg when the abdomen is opened, digital pressure or a clamp should be placed on the aorta at the diaphragmatic hiatus. After the source of hemorrhage is localized, direct digital occlusion (vascular injury) or laparotomy pad packing (solid organ injury) is used to control bleeding (Fig. 7-36). If the liver is the source in a hemodynamically unstable patient, additional control of bleeding is obtained by clamping the hepatic pedicle with a vascular clamp or Rummel tourniquet (Pringle maneuver) (Fig. 7-37). Similarly, clamping the splenic hilum may more effectively control bleeding than packing alone. When the spleen is mobilized, it should be gently rotated medially to expose the lateral peritoneum; this peritoneum and endoabdominal fascia are incised, which allows blunt

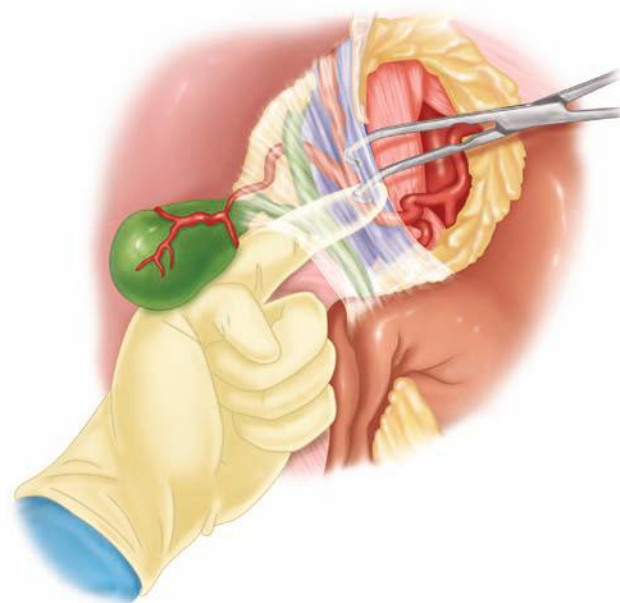


Figure 7-37. The Pringle maneuver, performed with a vascular clamp, occludes the hepatic pedicle containing the portal vein, hepatic artery, and common bile duct.

dissection of the spleen and pancreas as a composite from the retroperitoneum anterior to Gerota's fascia (Fig. 7-38).

Rapid exposure of the intra-abdominal vasculature can prove challenging in the face of exsanguinating hemorrhage. Proximal control of the aorta is obtained at the diaphragmatic hiatus; if an aortic injury is supraceliac, transecting the left crus of diaphragm or extending the laparotomy via a left thoracotomy may be necessary. The first decision is whether the patient has a supracolic or an infracolic vascular injury. Supracolic injuries (aorta, celiac axis, proximal superior mesenteric artery [SMA], and left renal arteries) are best approached a left medial visceral rotation (Fig. 7-39). This is done by incising the lateral peritoneal reflection (white line of Toldt) beginning at the distal descending colon and extending the incision along the colonic splenic flexure, around the posterior aspect of the spleen, and behind the gastric fundus, ending at the esophagus. The left

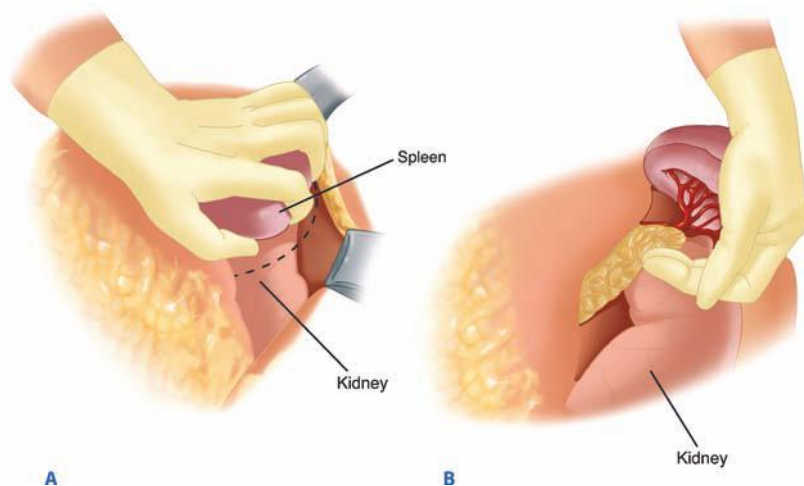


Figure 7-38. To mobilize the spleen, an incision is made into the endoabdominal fascia 1 cm lateral to the reflection of the peritoneum onto the spleen (A). While the spleen is gently rotated medially, a plane is developed between the pancreas and left kidney (B). With complete mobilization, the spleen can reach the level of the abdominal incision.

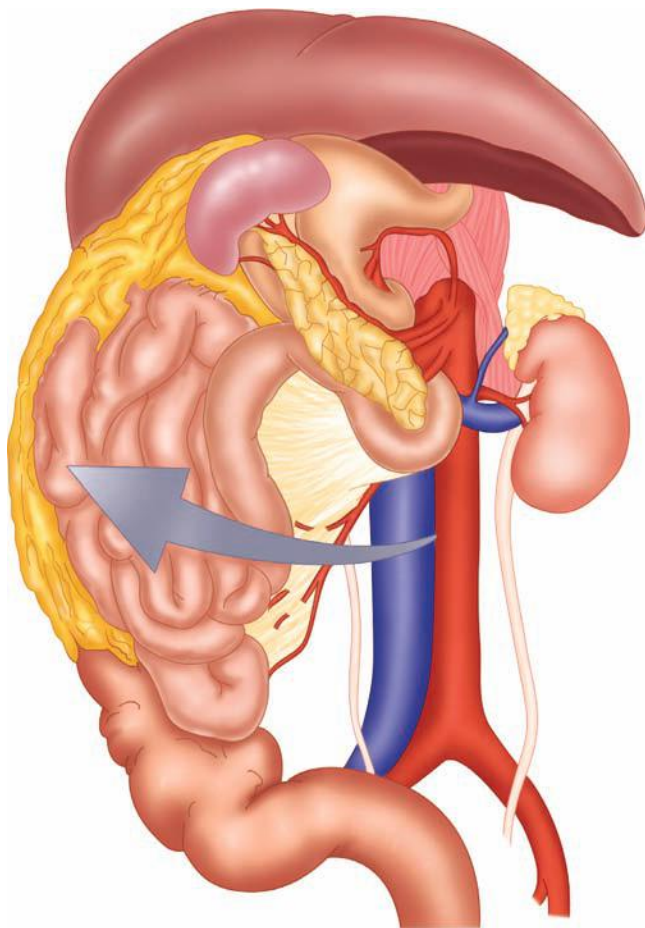


Figure 7-39. A left medial visceral rotation is used to expose the abdominal aorta.

colon, spleen, pancreas, and stomach are then rotated toward the midline. The authors prefer to leave the kidney in situ when mobilizing the viscera because this exaggerates the separation of the renal vessels from the SMA. The operative approach for SMA injuries is based on the level of injury. Fullen zone I SMA injuries, located posterior to the pancreas, are best exposed by a left medial visceral rotation. Fullen zone II SMA injuries, extending from the pancreatic edge to the middle colic branch, on the other hand, are approached via the lesser sac along the inferior edge of the pancreas at the base of the transverse mesocolon; the pancreatic body may be divided to gain proximal vascular access. More distal SMA injuries, Fullen zones III and IV, are approached directly within the mesentery. A venous injury behind the pancreas, from the junction of the superior mesenteric, splenic, and portal veins, is accessed by dividing the neck of the pancreas. Inferior vena cava injuries are approached by a right medial visceral rotation (Fig. 7-40). Proximal control is obtained just above the iliac bifurcation with direct pressure via a sponge stick; the injury is identified by cephalad dissection along the anterior surface of the inferior vena cava. A Satinsky clamp can be used to control anterior caval wounds.

Injuries of the iliac vessels pose a unique problem for emergent vascular control due to the number of vessels, their close proximity, and cross circulation. Proximal control at the infra-renal aorta arrests the arterial bleeding and avoids splanchnic and renal ischemia; however, venous injuries are not controlled with aortic clamping. Tamponade with a folded laparotomy pad

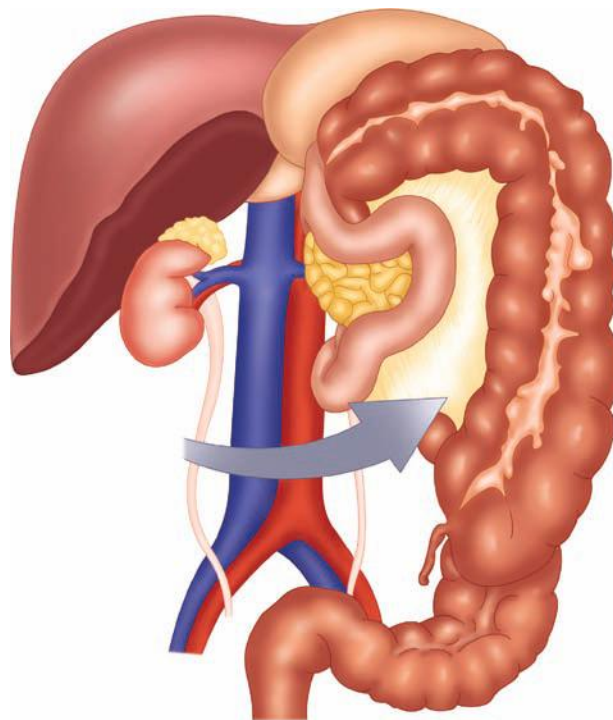


Figure 7-40. A right medial visceral rotation is used to expose the infrahepatic vena cava.

held directly over the bleeding site usually will establish hemostasis sufficient to prevent exsanguination. If hemostasis is not adequate to expose the vessel proximal and distal to the injury, sponge sticks can be strategically placed on either side of the injury and carefully adjusted to improve hemostasis. Alternatively, complete pelvic vascular isolation (Fig. 7-41) may be required to control hemorrhage for adequate visualization of the

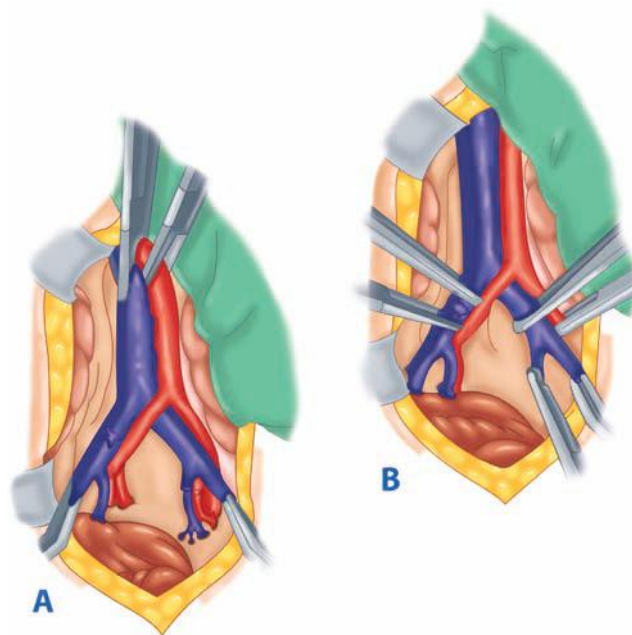


Figure 7-41. Pelvic vascular isolation. **A.** Initially, clamps are placed on the aorta, inferior vena cava, and bilateral external iliac vessels. **B.** With continued dissection, the clamps can be moved progressively closer to the vascular injury to limit unwarranted ischemia.

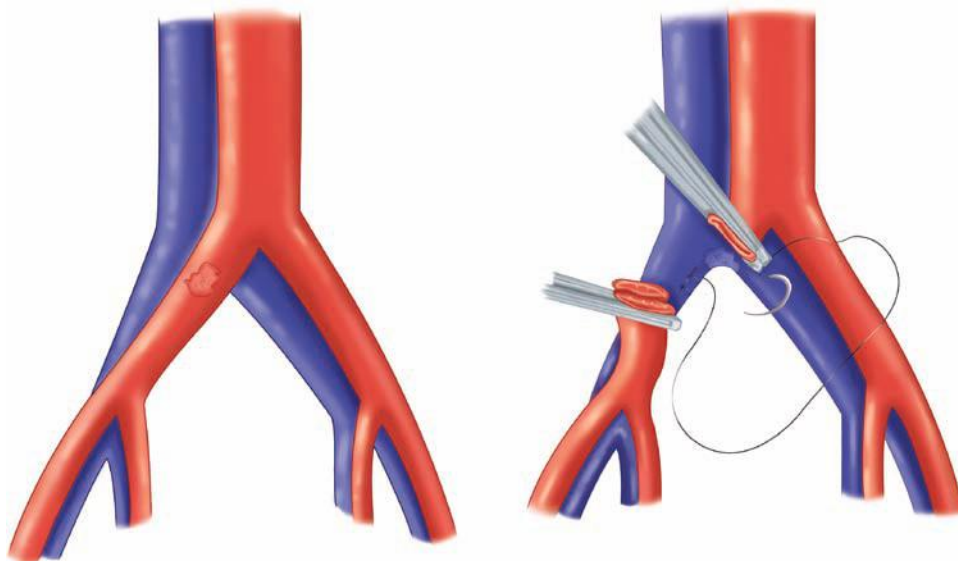


Figure 7-42. The right common iliac artery can be divided to expose the bifurcation of the inferior vena cava and the right common iliac vein.

injuries. The right common iliac artery obscures the bifurcation of the vena cava and the right iliac vein; the iliac artery may require division to expose venous injuries in this area (Fig. 7-42). The artery must be repaired after the venous injury is treated, however, because of limb-threatening ischemia.

Once overt hemorrhage is controlled, sources of enteric contamination are identified by serially running along the small and large bowel, looking at all surfaces. Associated hematomas should be unroofed to rule out adjacent bowel injury. The anterior and posterior aspects of the stomach should be inspected, which requires opening the lesser sac for complete visualization. Duodenal injuries should be evaluated with a wide Kocher maneuver. During exploration of the lesser sac, visualization and palpation of the pancreas is done to exclude injury. Palpating the anterior surface is not sufficient, because the investing fascia may mask a pancreatic injury; mobilization, including evaluation of the posterior aspect, is critical. After injuries are identified, whether to use damage control techniques or perform primary repair of injuries is based on the patient's intraoperative physiologic status (see sections, *Damage Control Surgery* and *Treatment of Specific Injuries*). In a patient with multisystem trauma, enteral access via gastrostomy tube or needle-catheter jejunostomy should be considered. If abdominal closure is indicated after the patient's injuries are addressed, the abdomen is irrigated with warm saline and the midline fascia is closed with a running heavy suture. The skin is closed selectively based on the amount of intra-abdominal contamination.

Vascular Repair Techniques Initial control of vascular injuries is accomplished digitally by applying enough direct pressure to stop the hemorrhage. Sharp dissection with fine scissors is used to define the injury and mobilize sufficient length for proximal and distal control. Fogarty thromboembolectomy should be done proximally and distally to optimize collateral blood flow. Heparinized saline (50 units/mL) is then injected into the proximal and distal ends of the injured vessel to prevent small clot formation on the exposed intima and media. Ragged edges of the injury site should be débrided using sharp dissection. Intravascular shunts are used when there are multiple life-threatening injuries or the arterial injury is anticipated to require saphenous vein interposition reconstruction.

Options for the treatment of vascular injuries are listed in Table 7-9. Arterial repair should always be done for the aorta, carotid, innominate, brachial, superior mesenteric, proper hepatic, renal, iliac, femoral, and popliteal arteries. Named arteries that usually tolerate ligation include the right or left hepatic artery and the celiac artery. In the lower extremities, at least one artery with distal runoff should be salvaged. Arterial injuries that may be treated nonoperatively include small pseudoaneurysms, intimal dissections, small intimal flaps, and small arteriovenous fistulas in the extremities. Follow-up imaging is performed 1 to 2 weeks after injury to confirm healing. Venous repair should be performed for injuries of the superior vena cava, the inferior vena cava proximal to the renal veins, and the portal vein, although the portal vein may be ligated in extreme cases. The SMV should be repaired optimally, but >80% of patients will survive following ligation. Similarly the left renal vein can usually be ligated adjacent to the IVC due to collateral decompression.

The type of operative repair for a vascular injury is based on the extent and location of injury. Lateral suture repair is preferred for arterial injuries with minimal loss of tissue. End-to-end

Table 7-9

Options for the treatment of vascular injuries

Observation
Ligation
Lateral suture repair
End-to-end primary anastomosis
Interposition grafts
Autogenous vein
Polytetrafluoroethylene graft
Dacron graft
Transpositions
Extra-anatomic bypass
Interventional radiology
Stents
Embolization

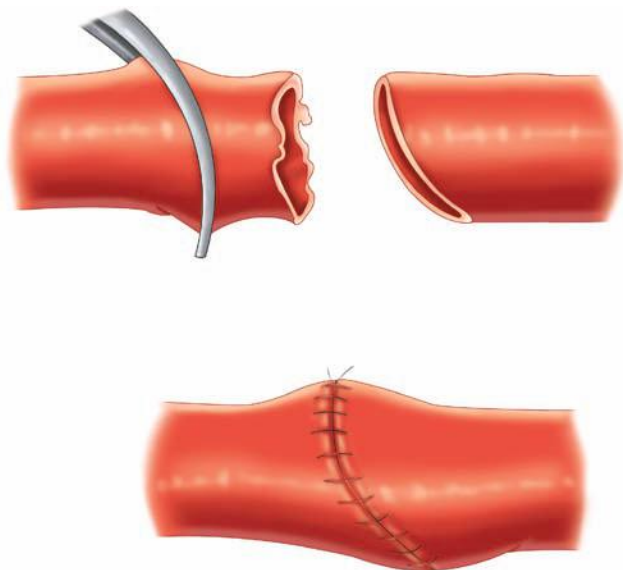


Figure 7-43. Small arteries repaired with an end-to-end anastomosis are prone to stricture. Enlarging the anastomosis by beveling the cut ends of the injured vessel can minimize this problem. A curved hemostat is a useful adjunct to create the curve.

primary anastomosis is performed if the vessel can be repaired without tension. Arterial defects of 1 to 2 cm often can be bridged by mobilizing the severed ends of the vessel after ligating small branches. The surgeon should not be reluctant to divide small branches to obtain additional length, because most injured patients have normal vasculature, and the preservation of potential collateral flow is not as important as in revascularization for atherosclerosis. The aorta, subclavian artery, and brachial artery, however, are difficult to mobilize for additional length. To avoid postoperative stenosis, particularly in smaller arteries, beveling or spatulation should be used so that the completed anastomosis is slightly larger in diameter than the native artery (Fig. 7-43). The authors emphasize the parachute technique to ensure precision placement of the posterior suture line (Fig. 7-44). If this technique is used, traction must be maintained on both ends of the suture, or leakage from the posterior aspect of the suture line may occur. A single temporary suture 180 degrees from the posterior row may be used to maintain alignment for challenging anastomoses.

Interposition grafts are used when end-to-end anastomosis cannot be accomplished without tension despite mobilization. For vessels <6 mm in diameter (e.g., internal carotid, brachial, superficial femoral, and popliteal arteries), autogenous saphenous vein from the contralateral groin should be used, because polytetrafluoroethylene (PTFE) grafts of <6 mm have a prohibitive rate of thrombosis. Larger arteries (e.g., subclavian, innominate, aorta, common iliac) are bridged by PTFE grafts. PTFE is preferred over Dacron because of the reported decreased risk of infection.⁶² Aortic or iliac arterial injuries may be complicated by enteric contamination from colon or small bowel injuries. There is a natural reluctance to place artificial grafts in such circumstances, but graft infections are rare and the time required to perform an axillofemoral bypass is excessive.⁶³ Therefore, after the control of hemorrhage, bowel contamination is contained and the abdomen irrigated before placing PTFE grafts.⁶⁴ After placement of the graft, it is covered with peritoneum or omentum before definitive treatment of the enteric injuries.

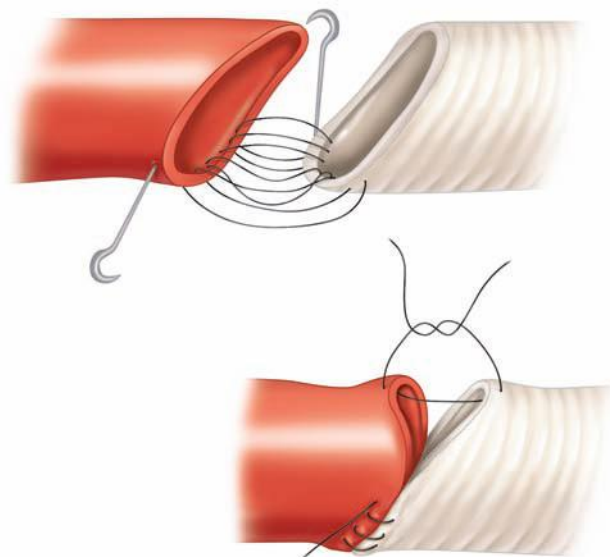


Figure 7-44. The parachute technique is helpful for accurate placement of the posterior sutures of an anastomosis when the arterial end is fixed and an interposition graft is necessary. Traction must be maintained on both ends of the suture to prevent loosening and leakage of blood. Six stitches should be placed before the graft is pulled down to the artery.

Transposition procedures can be used when an artery has a bifurcation and one vessel can be ligated safely. Injuries of the proximal internal carotid can be treated by mobilizing the adjacent external carotid, dividing it distal to the internal injury, and performing an end-to-end anastomosis between it and the distal internal carotid (Fig. 7-45). The proximal stump of the internal carotid is oversewn, with care taken to avoid a blind pocket where a clot may form. Injuries of the common and external iliac arteries can be handled in a similar fashion (Fig. 7-46), while maintaining flow in at least one internal iliac artery.

Venous injuries are inherently more difficult to reconstruct due to their propensity to thrombose. Small injuries without loss of tissue can be treated with lateral suture repair. More complex repairs with interposition grafts may thrombose but this typically occurs gradually over 1 to 2 weeks. During this time adequate collateral circulation develops, which is sufficient to avoid acute venous hypertension. Therefore, it is reasonable to use ringed PTFE for venous interposition grafting and accept a gradual, but eventual, thrombosis while allowing time for collateral circulation to develop. Such an approach is reasonable for venous injuries of the superior vena cava, suprarenal vena cava, SMV, and popliteal vein because ligation of these is associated with significant morbidity. In the remainder of venous injuries the vein may be ligated. In such patients, chronic venous hypertensive complications in the lower extremities often can be avoided by (a) temporary use of elastic bandages (Ace wraps) applied from the toes to the hips at the end of the procedure, and (b) temporary continuous elevation of the lower extremities to 30 to 45 degrees. These measures should be maintained for 1 week; if the patient has no peripheral edema with ambulation, these maneuvers are no longer required.

Damage Control Surgery

The recognition of the bloody vicious cycle and the introduction of damage control surgery (DCS) have improved the

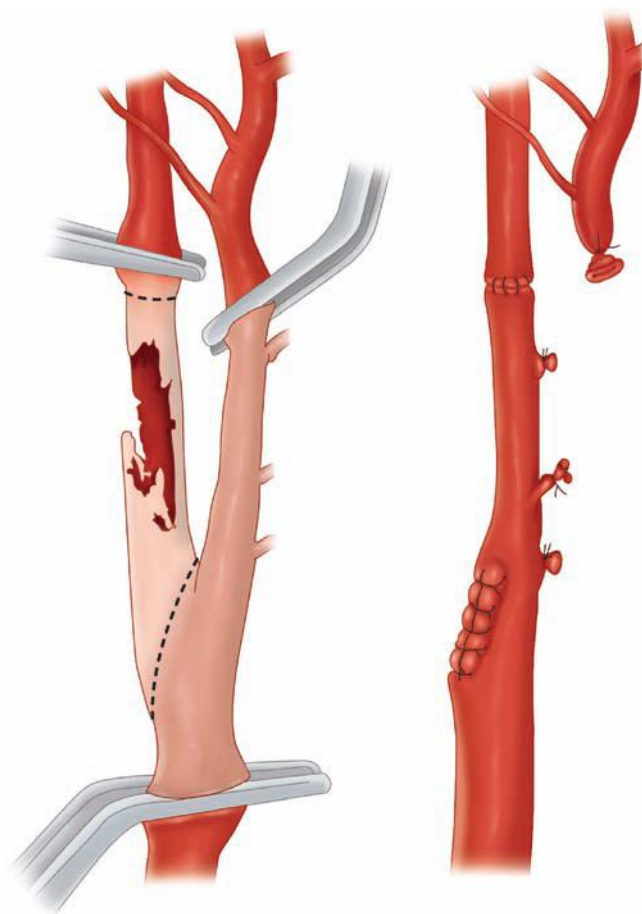


Figure 7-45. Carotid transposition is an effective approach for treating injuries of the proximal internal carotid artery.

survival of critically injured patients. Conceptually, the bloody vicious cycle, first described in 1981, is the lethal combination of coagulopathy, hypothermia, and metabolic acidosis (Fig. 7-47).⁴⁹ Hypothermia from evaporative and conductive heat loss and diminished heat production occurs despite the use of warming blankets and blood warmers. The metabolic acidosis of shock is exacerbated by aortic clamping, administration of vasopressors, massive RBC transfusions, and impaired myocardial performance. The acute coagulopathy of trauma, described previously, is compounded by hemodilution, hypothermia, and acidosis. Once the cycle starts, each component magnifies the other, which leads to a downward spiral and ultimately a fatal arrhythmia. The purpose of DCS is to limit operative time so that the patient can be returned to the SICU for physiologic restoration and the cycle thereby broken. Indications to limit the initial operation and institute DCS techniques include a combination of refractory hypothermia (temperature $<35^{\circ}\text{C}$), profound acidosis, (arterial pH <7.2 , base deficit <15 mmol/L), and refractory coagulopathy.^{49,65} The decision to abbreviate a trauma laparotomy is made intraoperatively as the patient's clinical course becomes clearer and laboratory values become available.⁶⁶

The goal of DCS is to control surgical bleeding and limit GI spillage. The operative techniques used are temporary measures, with definitive repair of injuries delayed until the patient is physiologically replete. Controlling surgical bleeding while preventing ischemia is of utmost importance during DCS. Aortic injuries must be repaired using an interposition PTFE graft. Although celiac artery injuries may be ligated, the SMA must maintain flow, and the early insertion of an intravascular shunt is advocated. Similarly, perfusion of the iliac system and infrainguinal vessels can be restored with a vascular shunt, with interposition graft placement delayed until hours later. Venous injuries are

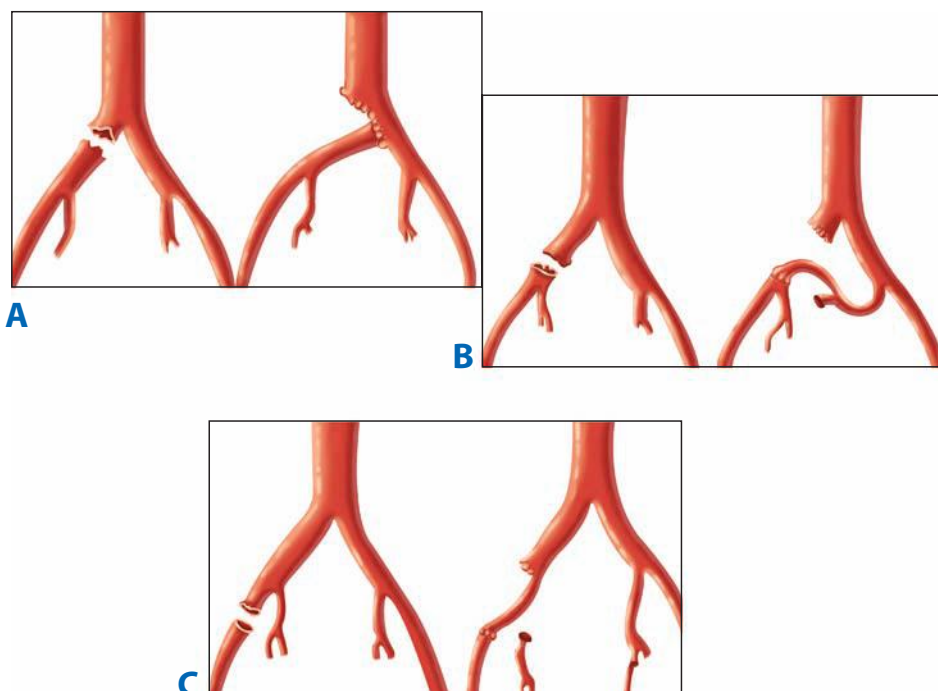


Figure 7-46. Transposition procedures can be used for iliac artery injuries to eliminate the dilemma of placing an interposition polytetrafluoroethylene graft in the presence of enteric contamination. **A.** Right common iliac artery transposed to left common iliac artery. **B.** Left internal iliac artery transposed to the distal right common iliac artery. **C.** Right internal iliac artery transposed to the right external iliac artery.

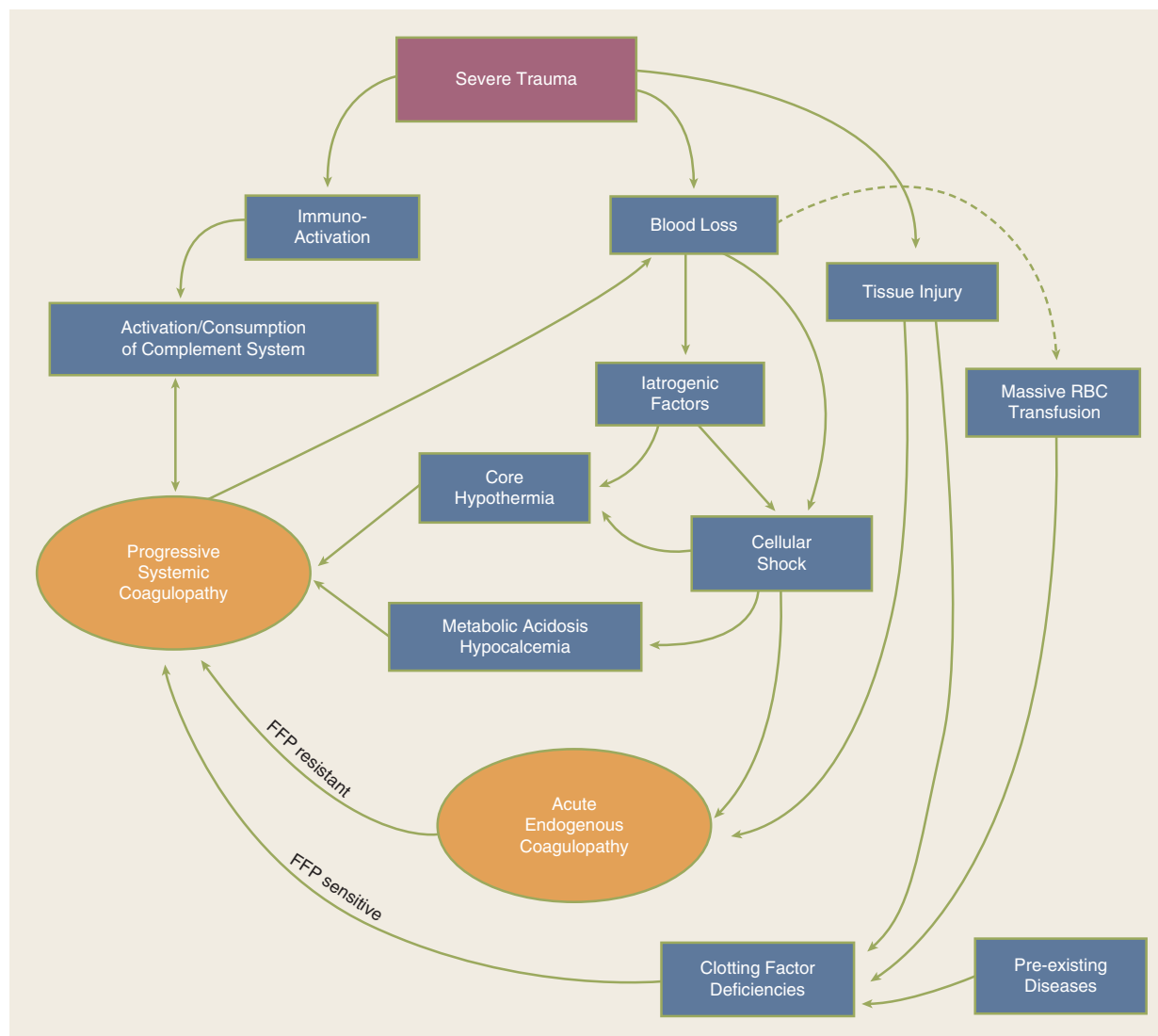


Figure 7-47. The bloody vicious cycle. FFP = fresh-frozen plasma; RBC = red blood cell.

preferentially treated with ligation in damage control situations, except for the suprarenal inferior vena cava and popliteal vein. For extensive solid organ injuries to the spleen or one kidney, excision is indicated rather than an attempt at operative repair. For hepatic injuries, perihepatic packing of the liver will usually

tamponade bleeding (see Fig. 7-36). Translobar gunshot wounds of the liver are best controlled with balloon catheter tamponade, whereas deep lacerations can be controlled with Foley catheter inflation deep within the injury track (Fig. 7-48). For thoracic injuries requiring DCS several options exist. For

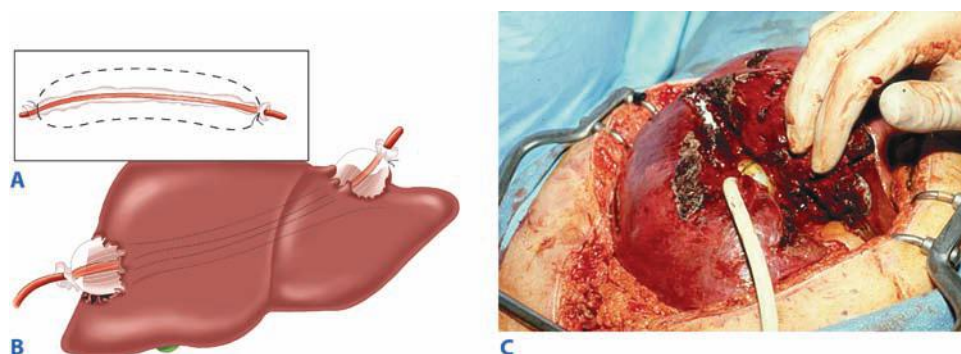


Figure 7-48. **A.** An intrahepatic balloon used to tamponade hemorrhage from transhepatic penetrating injuries is made by placing a red rubber catheter inside a 1-inch Penrose drain, with both ends of the Penrose drain ligated. **B.** Once placed inside the injury tract, the balloon is inflated with saline until hemorrhage stops. **C.** A Foley catheter with a 30-mL balloon can be used to halt hemorrhage from deep lacerations to the liver.

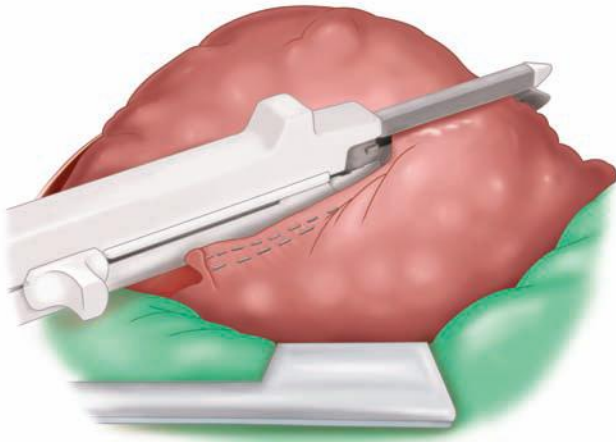


Figure 7-49. Pulmonary tractotomy divides the pulmonary parenchyma using either a transection/anastomosis (TA) or gastrointestinal anastomosis (GIA) stapler. The opened track permits direct access to injured vessels or bronchi for individual ligation.

bleeding peripheral pulmonary injuries, wedge resection using a stapler is performed. In penetrating injuries, pulmonary tractotomy is used to divide the parenchyma (Fig. 7-49); individual vessels and bronchi are then ligated using a 3-0 polydioxanone suture (PDS) and the track left open. Patients who sustain more proximal injuries may require formal pulmonary resection but pneumonectomy is poorly tolerated. Cardiac injuries may be temporarily controlled using a running 3-0 nonabsorbable polypropylene suture or skin staples. Pledged repair should be performed for the relatively thin right ventricle.

The second key component of DCS is limiting enteric content spillage. Small GI injuries (stomach, duodenum, small intestine, and colon) may be controlled using a rapid whipstitch of 2-0 polypropylene. Complete transection of the bowel or segmental damage is controlled using a GIA stapler, often with resection of the injured segment. Alternatively, open ends of the bowel may be ligated using umbilical tapes to limit spillage. Pancreatic injuries, regardless of location, are packed and the evaluation of ductal integrity postponed. Urologic injuries may require catheter diversion. Before the patient is returned to the SICU, the abdomen must be temporarily closed. Originally, penetrating towel clips were used to approximate the skin; however, the ensuing bowel edema often produces a delayed abdominal compartment syndrome. Currently, temporary closure of the abdomen is accomplished using an antimicrobial surgical incise drape (Ioban, 3M Health Care, St Paul, MN) (Fig. 7-50). In this technique, the bowel is covered with a fenestrated subfascial sterile drape (45 × 60 cm Steri-Drape 3M Health Care), and two Jackson-Pratt drains are placed along the fascial edges; this is then covered using an Ioban drape, which allows closed suction to control reperfusion-related ascitic fluid egress while providing adequate space for bowel expansion to prevent abdominal compartment syndrome. During the initial DCS stage, the subfascial sterile drape is not covered by a blue towel so that the status of the bowel and hemorrhage control can be assessed. Return to the OR within 24 hours is planned once the patient clinically improves, as evidenced by normothermia, normalization of coagulation test results, and correction of acidosis.

Head Injuries

Intracranial Injuries CT scanning, performed on all patients with a significant closed head injury (GCS score <14), identifies and quantitates intracranial lesions. Patients with intracranial hemorrhage, including epidural hematoma, subdural hematoma, subarachnoid hemorrhage, intracerebral hematoma or contusion, and diffuse axonal injury, are admitted to the SICU. In patients with abnormal findings on CT scans and GCS scores of ≤8, intracranial pressure (ICP) should be monitored using fiberoptic intraparenchymal devices or intraventricular catheters.²⁹ Although an ICP of 10 mm Hg is believed to be the upper limit of normal, therapy generally is not initiated until ICP is >20 mm Hg.²⁹ Indications for operative intervention to remove space-occupying hematomas are based on the clot volume, amount of midline shift, location of the clot, GCS score, and ICP.²⁹ A shift of >5 mm typically is considered an indication for evacuation, but this is not an absolute rule. Smaller hematomas that are in treacherous locations, such as the posterior fossa, may require drainage due to brain stem compression or impending herniation. Removal of small hematomas may also improve ICP and cerebral perfusion in patients with elevated ICP that is refractory to medical therapy. Patients with diffuse cerebral edema resulting in excessive ICP may require a decompressive craniectomy, although a recent AAST multicenter trial questions the benefits.^{67,68} Patients with open or depressed skull fractures, with or without sinus involvement, may require operative intervention. Penetrating injuries to the head require operative intervention for hemorrhage control, evacuation of blood, skull fracture fixation, or débridement.

General surgeons in communities without emergency neurosurgical coverage should have a working knowledge of burr hole placement in the event that emergent evacuation is required for a life-threatening epidural hematoma (Fig. 7-51).⁶⁹ The typical clinical course of an epidural hematoma is an initial loss of consciousness, a lucid interval, and recurrent loss of consciousness with an ipsilateral fixed and dilated pupil. While decompression of subdural hematomas may be delayed, epidural hematomas require evacuation within 70 minutes.⁶⁸ The final stages of this sequence are caused by blood accumulation that forces the temporal lobe medially, with resultant compression of the third cranial nerve and eventually the brain stem. The burr hole is made on the side of the dilated pupil to decompress the intracranial space. After stabilization, the patient is transferred to a facility with neurosurgical capability for formal craniotomy.

In addition to operative intervention, postinjury care directed at limiting secondary injury to the brain is critical. The goal of resuscitation and management in patients with head injuries is to avoid hypotension (SBP of <100 mm Hg) and hypoxia (partial pressure of arterial oxygen of <60 or arterial oxygen saturation of <90).²⁹ Attention, therefore, is focused on maintaining cerebral perfusion rather than merely lowering ICP. Resuscitation efforts aim for a euolemic state and an SBP of >100 mm Hg. Cerebral perfusion pressure (CPP) is equal to the mean arterial pressure minus the ICP, with a target range of >50 mm Hg.²⁹ CPP can be increased by either lowering ICP or raising mean arterial pressure. Sedation, osmotic diuresis, paralysis, ventricular drainage, and barbiturate coma are used in sequence, with coma induction being the last resort. The partial pressure of carbon dioxide (Pco₂) should be maintained in a normal range (35–40 mm Hg), but for temporary management of acute

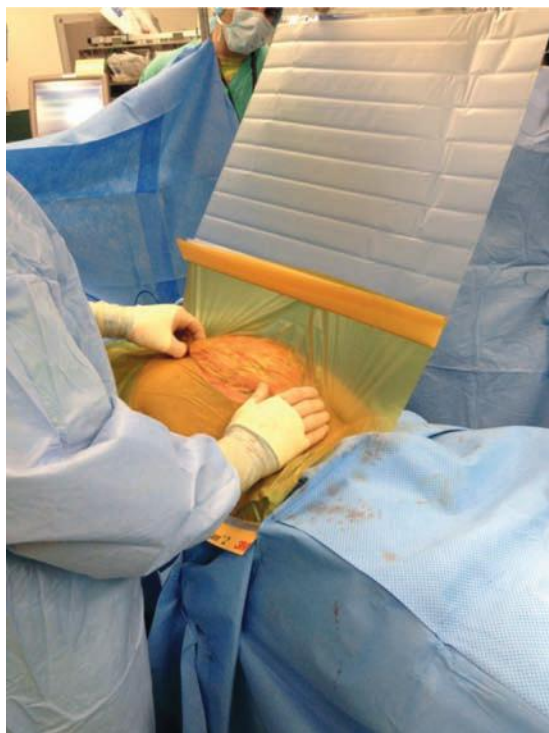
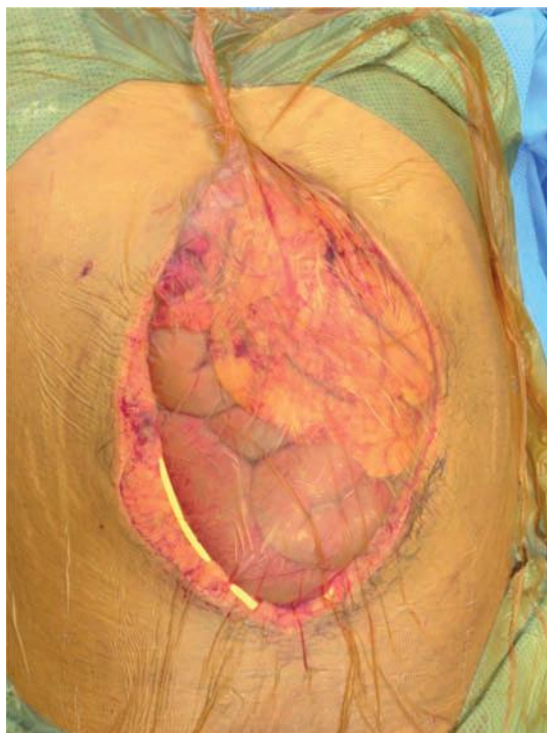
**A****B****C****D**

Figure 7-50. Temporary closure of the abdomen entails covering the bowel with a fenestrated subfascial 45 × 60 cm sterile drape (A), placing Jackson-Pratt drains along the fascial edge (B), and then occluding with an Ioban drape (C, D).

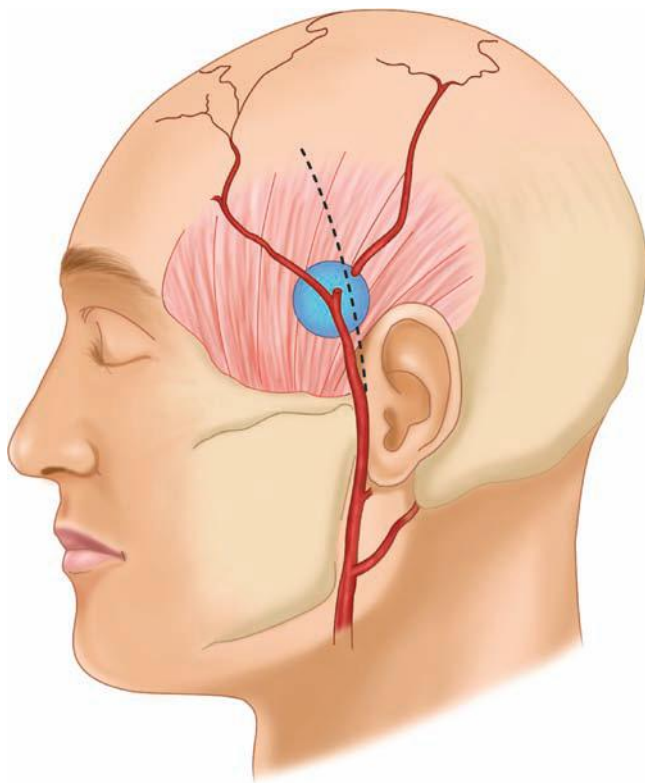


Figure 7-51. A burr hole is made for decompression of an epidural hematoma as a life-saving maneuver. One or more branches of the external carotid artery usually must be ligated to gain access to the skull. No attempt should be made to control intracranial hemorrhage through the burr hole. Rather, the patient's head should be wrapped with a bulky absorbent dressing and the patient transferred to a neurosurgeon for definitive care.

intracranial hypertension, inducing cerebral vasoconstriction by hyperventilation to a PCO_2 of <30 mm Hg is occasionally warranted. Moderate hypothermia (32° – 33° C [89.6° – 91.4° F]) has been proposed to improve neurologic outcomes when maintained for at least 48 hours, but studies to date have not validated this concept.^{29,70,71} Patients with intracranial hemorrhage should be monitored for postinjury seizures, and prophylactic anticonvulsant therapy (e.g., phenytoin [dilantin]) is indicated for 7 days after injury.^{29, 72}

Maxillofacial Injuries Maxillofacial injuries are common with multisystem trauma and require coordinated management by the trauma surgeon and the specialists in otolaryngology, plastic surgery, ophthalmology, and oral and maxillofacial surgery. Delay in addressing these systems that control vision, hearing, smelling, breathing, eating, and phonation may produce dysfunction and disfigurement with serious psychological impact. The maxillofacial complex is divided into three regions; the *upper face* containing the frontal sinus and brain, the *mid-face* containing the orbits, nose, and zygomaticomaxillary complex, and the *lower face* containing the mandible. High-impact kinetic energy is required to fracture the frontal sinus, orbital rims, and mandible, whereas low-impact forces will injure the nasal bones and zygoma.

The most common scenario, which at times may be life-threatening, is bleeding from facial fractures.⁷³ Temporizing measures include nasal packing, Foley catheter tamponade of

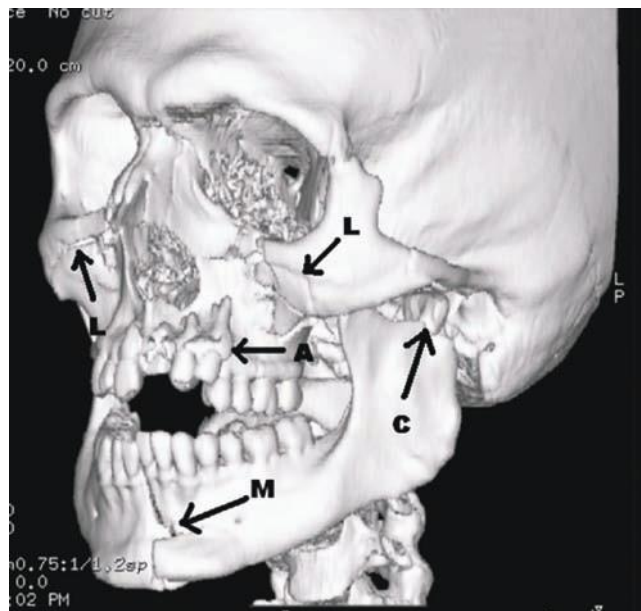


Figure 7-52. Three-dimensional computed tomographic scan illustrating Le Fort II maxillary (L) and alveolar (A) fractures, and fracture of the mandible (M) at the midline and at the weaker condyle (C). (Image used with permission from Vincent D. Eusterman, MD, DDS.)

posterior nasal bleeding, and oropharyngeal packing. Prompt angioembolization will halt exsanguinating hemorrhage. Fractures of tooth-bearing bone are considered open fractures and require antibiotic therapy and semiurgent repair to preserve the airway as well as the functional integrity of the occlusion (bite) and the aesthetics of the face. Orbital fractures may compromise vision, produce muscle injury causing diplopia, or change orbital volume to produce a sunken appearance to the orbit. Nose and nasoethmoidal fractures should be assessed carefully to identify damage to the lacrimal drainage system or to the cribriform plate producing cerebrospinal fluid rhinorrhea. After initial stabilization, a systematic physical examination of the head and neck should be performed that also includes cranial nerve examination and three-dimensional CT scanning of the maxillofacial complex (Fig. 7-52).

Cervical Injuries

Spine Treatment of injuries to the cervical spine is based on the level of injury, the stability of the spine, the presence of subluxation, the extent of angulation, the level of neurologic deficit, and the overall condition of the patient. In general, physician-supervised axial traction, via cervical tongs or the more commonly used halo vest, is used to reduce subluxations and stabilize the injury. Immobilization of injuries also is achieved with spinal orthoses (braces), particularly in those with associated thoracolumbar injuries. Surgical fusion typically is performed in patients with neurologic deficit, those with angulation of >11 degrees or translation of >3.5 mm, and those who remain unstable after halo placement. Indications for immediate operative intervention are deterioration in neurologic function and fractures or dislocations with incomplete deficit. Historically, methylprednisolone was administered to patients with acute spinal cord injury after blunt injury, with clinical data suggesting

a small benefit to initiating a 24-hour infusion if started within 3 hours and a 48-hour infusion if started 3 to 8 hours.⁷⁴ Current guidelines, however, no longer recommend steroids for acute injuries.⁷⁵ The role and timing of operative surgical decompression after acute spinal cord injury is debated. However, evidence supports urgent decompression of bilateral locked facets in patients with incomplete tetraplegia or with neurologic deterioration. Urgent decompression in acute cervical spinal cord injury is safe. Performing surgery within 24 hours may decrease length of stay and complications.⁷⁶ Complete injuries of the spinal cord remain essentially untreatable. Yet, approximately 3% of patients who present with flaccid quadriplegia have concussive injuries, and these patients represent the very few who seem to have miraculous recoveries.

Vascular Cervical vascular injuries due to either blunt or penetrating trauma can result in devastating neurologic sequelae or exsanguination. Penetrating injuries to the carotid artery and internal jugular vein usually are obvious on operative neck exploration. The principles of vascular repair techniques (discussed previously) apply to carotid injuries, and options for repair include end-to-end primary repair (often possible with mobilization of the common carotid), graft interposition, and transposition procedures. All carotid injuries should be repaired except in patients who present in coma with a delay in transport. Prompt revascularization of the internal carotid artery, using a

temporary Pruitt-Inahara shunt, should be considered in patients arriving in profound shock. Otherwise, carotid shunting should be done selectively as in elective carotid endarterectomy but the patient should be systemically anticoagulated. Currently, we administer heparin with an ACT target of 250 sec. Tangential wounds of the internal jugular vein should be repaired by lateral venorrhaphy, but extensive wounds are efficiently addressed by ligation. However, it is not advisable to ligate both jugular veins due to potential intracranial hypertension. Vertebral artery injuries due to penetrating trauma are difficult to control operatively because of the artery's protected location within the foramen transversarium. Although exposure from an anterior approach can be accomplished by removing the anterior elements of the bony canal and the tough fascia covering the artery between the elements, typically the most efficacious control of such injuries is angioembolization. Fogarty catheter balloon occlusion, however, is useful for controlling acute bleeding if encountered during neck exploration.

Blunt injury to the carotid or vertebral arteries may cause dissection, thrombosis, or pseudoaneurysm, typically in the surgically inaccessible distal internal carotid (Fig. 7-53).⁷⁷ Early recognition and management of these injuries is paramount, because patients treated with antithrombotics have a stroke rate of <1% compared with stroke rates of 20% in untreated patients. Because treatment must be instituted during the latent period

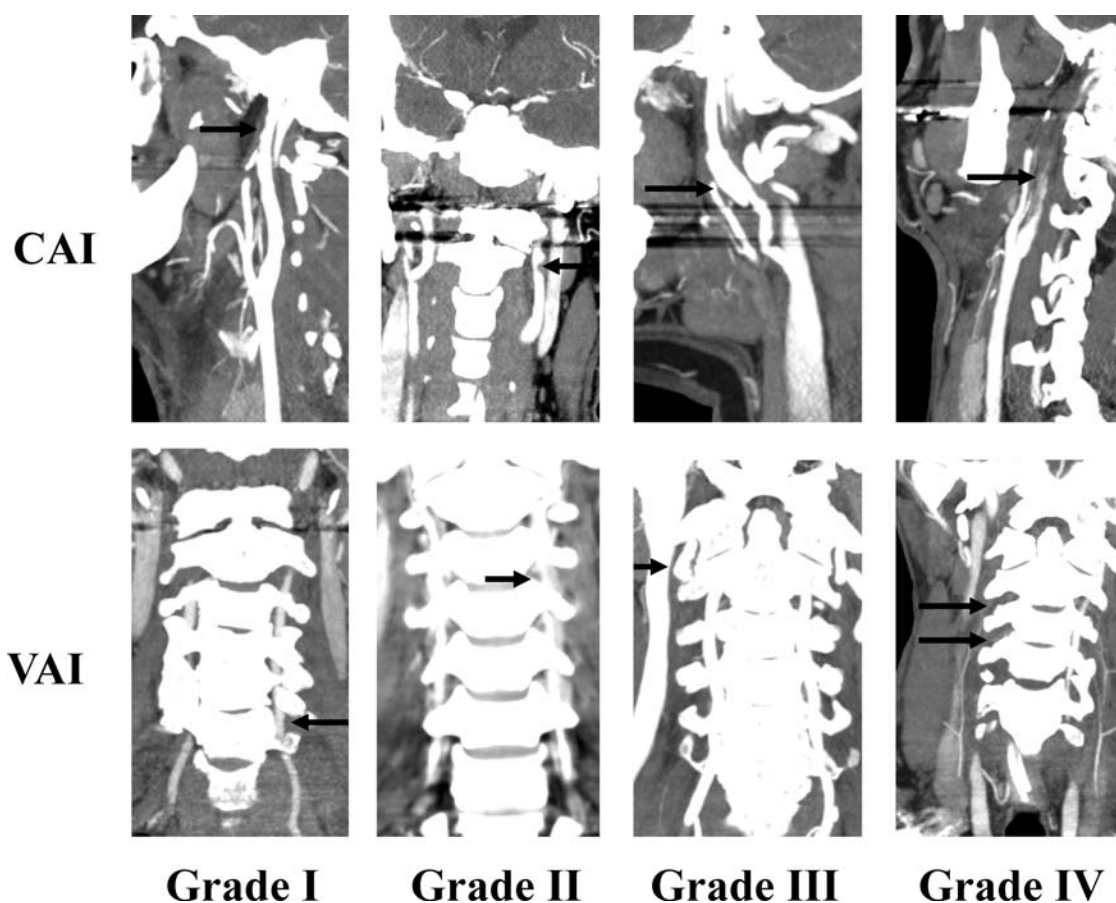


Figure 7-53. The Denver grading scale for blunt cerebrovascular injuries. Grade I: irregularity of the vessel wall, dissection/intramural hematoma with <25% luminal stenosis. Grade II: visualized intraluminal thrombus or raised intimal flap, or dissection/intramural hematoma with 25% or more luminal narrowing. Grade III: pseudoaneurysm. Grade IV: vessel occlusion. Grade V: vessel transection. CAI = carotid artery injury; VAI = vertebral artery injury.

9► between injury and onset of neurologic sequelae, diagnostic imaging is performed based on identified risk factors (Fig. 7-54).⁷⁸ After identification of an injury, antithrombotics are administered if the patient does not have contraindications (intracranial hemorrhage, falling hemoglobin level with solid organ injury or pelvic fracture). Heparin, started without a loading dose at 15 units/kg per hour, is titrated to achieve a PTT between 40 and 50 seconds or antiplatelet agents are initiated

(aspirin 325 mg/d or clopidogrel 75 mg/d). The types of antithrombotic treatment appear equivalent in published studies to date, and the duration of treatment is empirically recommended to be 6 months.^{79,80} The role of carotid stenting for grade III internal carotid artery injuries remain controversial. Thrombosis of the internal jugular veins caused by blunt trauma can occur unilaterally or bilaterally and is often discovered incidentally, because most patients are asymptomatic. Bilateral thrombosis

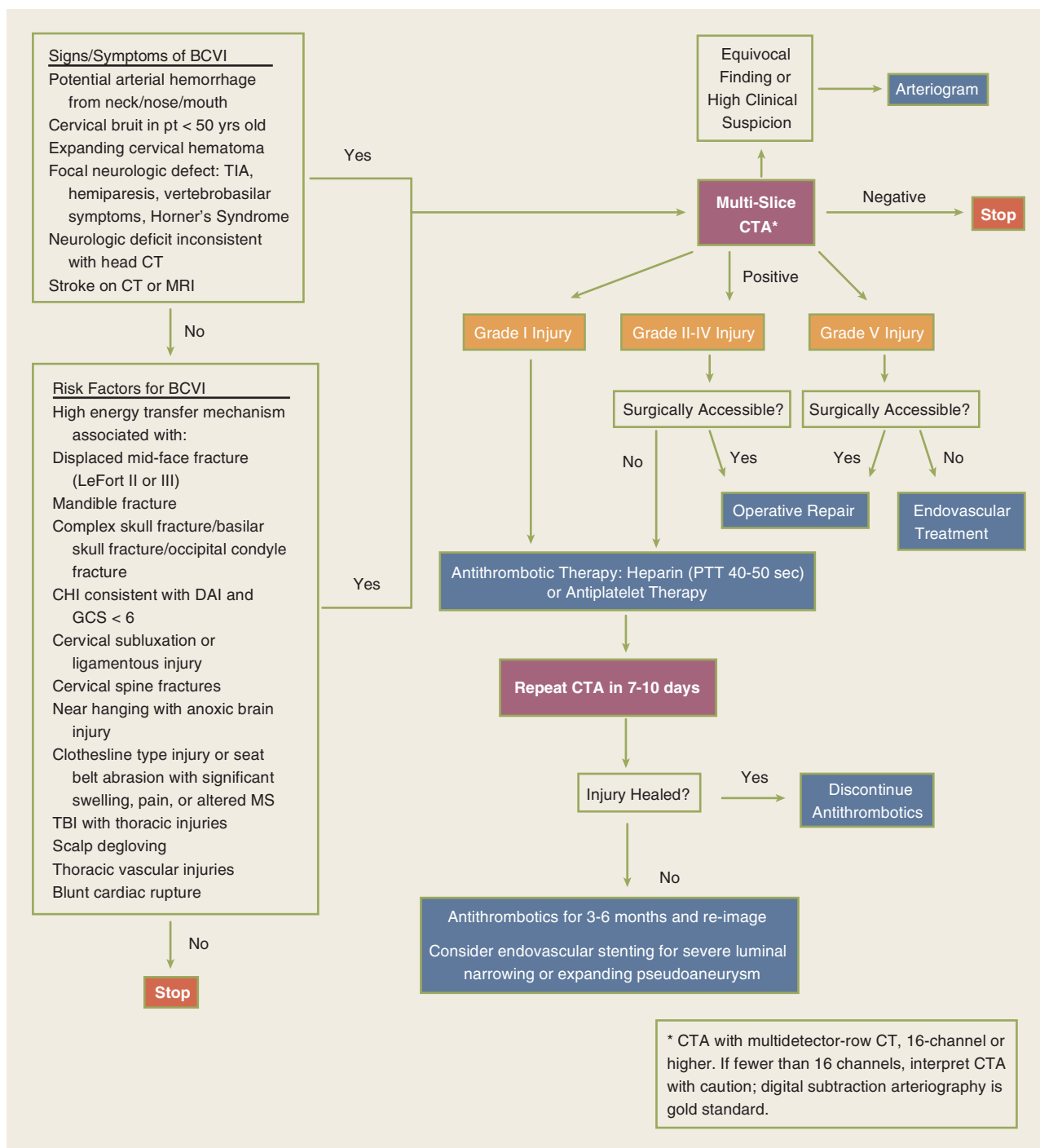


Figure 7-54. Screening and treatment algorithm for blunt cerebrovascular injuries (BCVIs). Angio = angiography; ASA = acetylsalicylic acid; BRB = bright red blood; CHI = closed head injury; C-spine = cervical spine; CT = computed tomography; DAI = diffuse axonal injury; GCS = Glasgow Coma Scale score; MRI = magnetic resonance imaging; MS = mental status; Neg = negative; pt = patient; PTT = partial thromboplastin time; TIA = transient ischemic attack.

can aggravate cerebral edema in patients with serious head injuries; stent placement should be considered in such patients if ICP remains elevated.

Aerodigestive Subclinical fractures of the larynx and trachea may manifest as cervical emphysema. Fractures documented by CT scan are usually repaired. Common injuries include thyroid cartilage fractures, rupture of the thyroepiglottic ligament, disruption of the arytenoids or vocal cord tears, and cricoid fractures. After débridement of devitalized tissue, tracheal injuries are repaired end-to-end using a single layer of interrupted absorbable sutures. Associated injuries of the esophagus are common in penetrating injuries due to its close proximity. After débridement and repair, vascularized tissue is interposed between the repaired esophagus and trachea, and a closed suction drain is placed. The sternocleidomastoid muscle or strap muscles are useful for interposition and help prevent postoperative fistulas.

Chest Injuries

The most common injuries from both blunt and penetrating thoracic trauma are hemothorax and pneumothorax. More than 85% of patients can be definitively treated with a chest tube. The indications for thoracotomy include significant initial or ongoing hemorrhage from the tube thoracostomy and specific imaging-identified diagnoses (Table 7-10). One caveat concerns the patient who presents after a delay. Even when the initial chest tube output is 1.5 L, if the output ceases and the lung is re-expanded, the patient may be managed nonoperatively if hemodynamically stable.

Great Vessels Over 90% of thoracic great vessel injuries are due to penetrating trauma, although blunt injury to the innominate, subclavian, or descending aorta may cause a pseudoaneurysm or frank rupture.^{40,81,82} Simple lacerations of the ascending or transverse aortic arch can be repaired with lateral aortorrhaphy. Repair of posterior injuries, or those requiring interposition grafting of the arch, require full cardiopulmonary bypass, and repair of complex injuries may require circulatory arrest. Innominate artery injuries are repaired using the bypass exclusion technique,⁸² which avoids the need for cardiopulmonary

Table 7-10

Indications for operative treatment of thoracic injuries

- Initial tube thoracostomy drainage of >1000 mL (penetrating injury) or >1500 mL (blunt injury)
- Ongoing tube thoracostomy drainage of >200 mL/h for 3 consecutive hours in noncoagulopathic patients
- Caked hemothorax despite placement of two chest tubes
- Selected descending torn aortas
- Great vessel injury (endovascular techniques may be used in selected patients)
- Pericardial tamponade
- Cardiac herniation
- Massive air leak from the chest tube with inadequate ventilation
- Tracheal or main stem bronchial injury diagnosed by endoscopy or imaging
- Open pneumothorax
- Esophageal perforation
- Air embolism

bypass. Bypass grafting from the proximal aorta to the distal innominate with a prosthetic tube graft is performed before the postinjury hematoma is entered. The PTFE graft is anastomosed end to side from the proximal undamaged aorta and anastomosed end-to-end to the innominate artery (Fig. 7-55). The origin of the innominate is then oversewn at its base to exclude the pseudoaneurysm or other injury. Subclavian artery injuries can be repaired using lateral arteriorrhaphy or PTFE graft interposition; due to its multiple branches and tethering of the artery, end-to-end anastomosis is not advocated if there is a significant segmental loss.

Descending thoracic aortic injuries may require urgent if not emergent intervention. However, operative intervention for intracranial or intra-abdominal hemorrhage or unstable pelvic fractures takes precedence. To prevent aortic rupture,

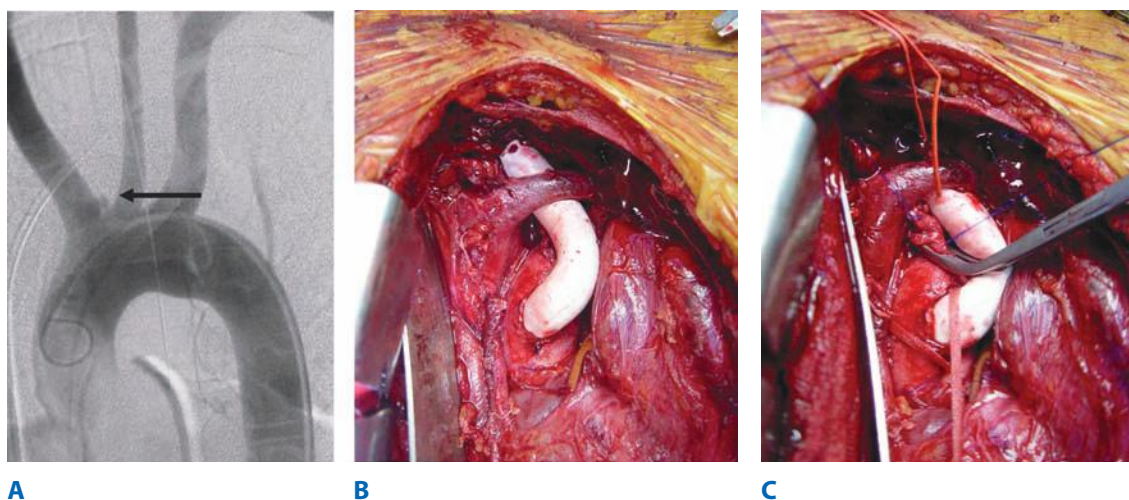


Figure 7-55. **A.** Angiography reveals a 1-cm pseudoaneurysm of the innominate artery origin. **B.** In the first stage of the bypass exclusion technique, a 12-mm polytetrafluoroethylene graft is anastomosed end to side from the proximal undamaged aorta, tunneled under the vein, and anastomosed end to end to the innominate artery. **C.** The origin of the innominate is then oversewn at its base to exclude the pseudoaneurysm.

pharmacologic therapy with a selective β_1 antagonist, esmolol, should be instituted in the trauma bay, with a target SBP of <100 mm Hg and heart rate of <100/min.^{36,83} Endovascular stenting is now the mainstay of treatment, but open operative reconstruction is warranted, or necessary, in select patients.^{84,85} Endovascular techniques are particularly appropriate in patients who cannot tolerate single lung ventilation, patients >60- years-old who are at risk for cardiac decompensation with aortic clamping, or patients with uncontrolled intracranial hypertension. While endograft sizing has improved, the major question is long-term outcome in younger patients. Open repair of the descending aorta is accomplished using partial left heart bypass.⁸⁶ With the patient in a right lateral decubitus position, the patient's hips and legs are rotated 45 degrees toward the supine position to gain access to the left groin for common femoral artery cannulation. Using a left posterolateral thoracotomy, the fourth rib is transected to expose the aortic arch and left pulmonary hilum. Partial left heart bypass is performed by cannulating the superior pulmonary vein with return through the left common femoral artery (Fig. 7-56). A centrifugal pump is used to provide flow rates of 2.5 to 4 L/min to maintain a distal perfusion pressure of >65 mm Hg. This prevents ischemic injury of the spinal cord as well as the splanchnic bed, and reduces left ventricular afterload.³⁶ Heparinization is not required, a significant benefit in patients with multiple injuries, particularly in those with intracranial hemorrhage. Unless contraindicated, however, low-dose heparin (100 units/kg) typically is administered to a target ACT of 250 sec to prevent thromboembolic events. Once bypass is initiated, vascular clamps are applied on the aorta between the left common carotid and left subclavian arteries, on the left subclavian, and on the aorta distal to the injury. In most patients a short PTFE graft (usually 18 mm in diameter) is placed using a running 3-0 polypropylene suture. However, primary arterial repair should be done when possible. Air and thrombus are flushed from the aortic graft before the final suture is tied, and the occluding vascular clamps are removed. The patient is then weaned from the centrifugal pump, the cannulas are removed, and primary repair of the cannulated vessels is performed. Removal of air or potential clot in the pulmonary vein is important during decannulation to avoid left heart emboli to the systemic circulation.

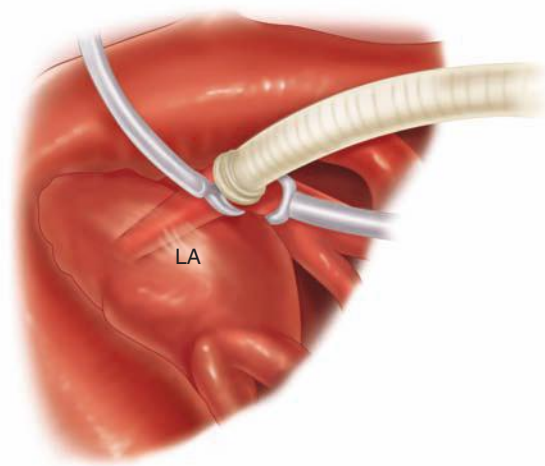


Figure 7-56. When repairing a tear of the descending thoracic aorta, perfusion of the spinal cord while the aorta is clamped is achieved by using partial left heart bypass. The venous cannula is inserted into the left superior pulmonary vein because it is less prone to tearing than the left atrium (LA).

Heart Blunt and penetrating cardiac injuries have widely differing presentations and therefore disparate treatments. Survivable penetrating cardiac injuries consist of wounds that can be repaired operatively; most are stab wounds. Before repair of the injury is attempted, hemorrhage should be controlled; injuries to the atria can be clamped with a Satinsky vascular clamp, whereas digital pressure is used to occlude the majority of ventricular wounds. Foley catheter occlusion of larger stellate lesions may be effective, but even minimal traction may enlarge the original injury. Temporary control of hemorrhage, and at times definitive repair, may be accomplished with skin staples for left ventricular lacerations; the myocardial edges of the laceration must coapt in diastole for stapling to be technically feasible. Definitive repair of cardiac injuries is performed with either running 3-0 polypropylene suture or interrupted, pledgeted 2-0 polypropylene suture (Fig. 7-57).⁸⁷ Use of

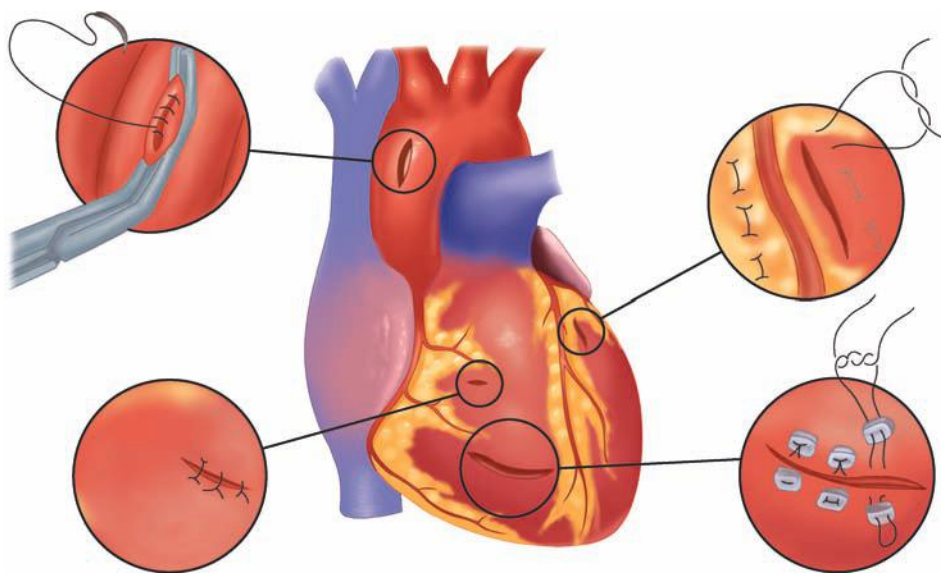


Figure 7-57. A variety of techniques may be necessary to repair cardiac wounds. Generally, pledget support is used for the relatively thin-walled right ventricle.

pledgets may be particularly important in the right ventricle to prevent sutures from pulling through the thinner myocardium. Injuries adjacent to coronary arteries should be repaired using horizontal mattress sutures, because use of running sutures results in coronary occlusion and distal infarction. Gunshot wounds may result in stellate lesions or contused, extremely friable myocardium adjacent to the wound. When the edges of such complex wounds cannot be fully approximated and hence the repair is not hemostatic, the authors have used surgical adhesive (BioGlue) to achieve hemostasis.⁸⁸ Occasionally, interior structures of the heart may be damaged. Intraoperative auscultation or postoperative hemodynamic assessment usually identifies such injuries.⁸⁹ Echocardiography (ECHO) can diagnose the injury and quantitate its effect on cardiac output. Immediate repair of valvular damage or septal defects rarely is necessary and would require cardiopulmonary bypass, but structural intracardiac lesions may progress and, thus, patients must have a follow-up ECHO.

Patients with blunt cardiac injury typically present with persistent tachycardia or conduction disturbances, but occasionally present with tamponade due to atrial or right ventricular rupture. There are no pathognomonic ECG findings, and cardiac enzyme levels do not correlate with the risk of cardiac complications.²³ Therefore, patients for whom there is high clinical suspicion of cardiac contusion and who are hemodynamically stable should be monitored for dysrhythmias for 24 hours by telemetry. Patients with hemodynamic instability should undergo ECHO to evaluate for wall motion abnormalities, pericardial fluid, valvular dysfunction, chordae rupture, or diminished ejection fraction. If such findings are noted or if vasoactive agents are required, cardiac function can be continuously monitored using a pulmonary artery catheter and serial SICU transthoracic or transesophageal ECHO.

Trachea, Bronchi, and Lung Parenchyma Less than 1% of all injured patients sustain intrathoracic tracheobronchial injuries, and only a small number require operative intervention. Although penetrating injuries may occur throughout the tracheobronchial system, blunt injuries most commonly occur within 2.5 cm of the carina. For patients with a massive air leak requiring emergent exploration, initial control of the injury to provide effective ventilation is obtained by passing an endotracheal tube either beyond the injury or into the contralateral mainstem bronchus. Principles of repair are similar to those for repair of cervical tracheal injuries. Devitalized tissue is débrided, and primary end-to-end anastomosis with 3-0 PDS suture is performed. Dissection should be limited to the area of injury to prevent disruption of surrounding bronchial vasculature and ensuing ischemia and stricture. Suture lines should be encircled with vascularized tissue, either pericardium, intercostal muscle, or pleura. Expectant management is employed for bronchial injuries that are less than one-third the circumference of the airway and have no evidence of a persistent major air leak.^{11,12} In patients with peripheral bronchial injuries, indicated by persistent air leaks from the chest tube and documented by endoscopy, bronchoscopically directed fibrin glue sealing may be useful.

The majority of pulmonary parenchymal injuries are suspected based upon identification of a pneumothorax; the vast majority is managed by tube thoracostomy. Identified parenchymal injuries encountered during thoracic exploration for a massive hemothorax are managed without resection as much

as possible. Peripheral lacerations with persistent bleeding can be managed with stapled wedge resection using a stapler. For central injuries, the current treatment is pulmonary tractotomy, which permits selective ligation of individual bronchioles and bleeders, prevents the development of an intraparenchymal hematoma or air embolism, and reduces the need for formal lobar resection (see Fig. 7-49).^{90,91} A stapling device, preferably the longest stapler available, is inserted directly into the injury track and positioned along the thinnest section of overlying parenchyma. The injury track is thus filleted open, which allows direct access to the bleeding vessels and leaking bronchi. The majority of injuries are definitively managed with selective ligation, and the defect is left open. Occasionally, tractotomy reveals a more proximal vascular injury that must be treated with formal lobectomy. Injuries severe enough to mandate pneumonectomy usually are fatal because of right heart decompensation.⁹²

One parenchymal injury that may be discovered during thoracic imaging is a posttraumatic pulmonary pseudocyst, colloquially termed a *pneumatocele*.⁹³ Traumatic pneumatoceles typically follow a benign clinical course and are treated with aggressive pain management, pulmonary toilet, and serial chest radiography to monitor for resolution of the lesion. If the patient has persistent fever or leukocytosis, however, chest CT is done to evaluate for an evolving abscess, because pneumatoceles may become infected. CT-guided catheter drainage may be required in such cases, because 25% of patients do not respond to antibiotic therapy alone. Surgery, ranging from partial resection to anatomic lobectomy, is indicated for unresolving complex pneumatoceles or infected lesions refractory to antibiotic therapy and drainage.

The most common complication after thoracic injury is development of an empyema. Management is based on CT diagnostic criteria.⁹⁴ Percutaneous drainage is indicated for a single loculation without appreciable rind. While fibrinolytics are often used for empyema there is a paucity of data to support their use. Early decortication via video-assisted thoracic surgery should be done promptly in patients with multiple loculations or a pleural rind of >1 cm.⁹⁵ Antibiotic treatment is based on definitive culture results, but presumptive antibiotics should cover MRSA in the SICU.

Esophagus Due to the proximity of the structures, esophageal injuries often occur with tracheobronchial injuries, particularly in cases of penetrating trauma. Operative options are based on the extent and location of esophageal injury. With sufficient mobilization, a primary single-layer end-to-end anastomosis may be performed after appropriate débridement. As with cervical repairs, if there are two suture lines in close approximation (trachea or bronchi and esophagus) interposition of a vascularized pedicle is warranted to prevent fistula formation. Perforations at the gastroesophageal junction may be treated with repair and Nissan fundoplication or, for destructive injuries, segmental resection and gastric pull-up. With large destructive injuries or delayed presentation of injuries, esophageal exclusion with wide drainage, diverting loop esophagostomy, and placement of a gastrostomy tube should be considered.

Chest Wall and Diaphragm Virtually all chest wall injuries, consisting of rib fractures and laceration of intercostal vessels, are treated nonoperatively with pain control, pulmonary toilet or ventilatory management, and drainage of the pleural

space as indicated. Early institution of effective pain control is essential. The authors advocate pre-emptive rib blocks with 0.25% bupivacaine hydrochloride (Marcaine) in the trauma bay, followed by thoracic wall pain catheters.⁹⁶ Epidural anesthesia is reserved for multiple segmental fractures. Persistent hemorrhage from a chest tube after blunt trauma most often is due to injured intercostal arteries; for unusual persistent bleeding (see Table 7-10), thoracotomy with direct ligation or angioembolization may be required to arrest hemorrhage. In cases of extensive flail chest segments or markedly displaced rib fractures, open reduction and internal fixation of the fracture with plates may be warranted. The current role of operative rib fixation remains controversial. Chest wall defects, particularly those seen with open pneumothorax, are repaired using local approximation of tissues or tissue transfer for coverage. Scapular and sternal fractures rarely require operative intervention but are markers for significant thoracoabdominal force during injury; significant displacement may benefit from sternal plating (Fig. 7-58). Careful examination and imaging should exclude associated injuries, including blunt cardiac injury and descending aortic tears. On the other hand, clavicle fractures often are isolated injuries and should be managed with pain control and immobilization. The exception is posterior dislocation of the clavicular head, which may injure the subclavian vessels.

Blunt diaphragmatic injuries usually result in a linear tear, and most injuries are large, whereas penetrating injuries are variable in size and location depending on the agent of injury.

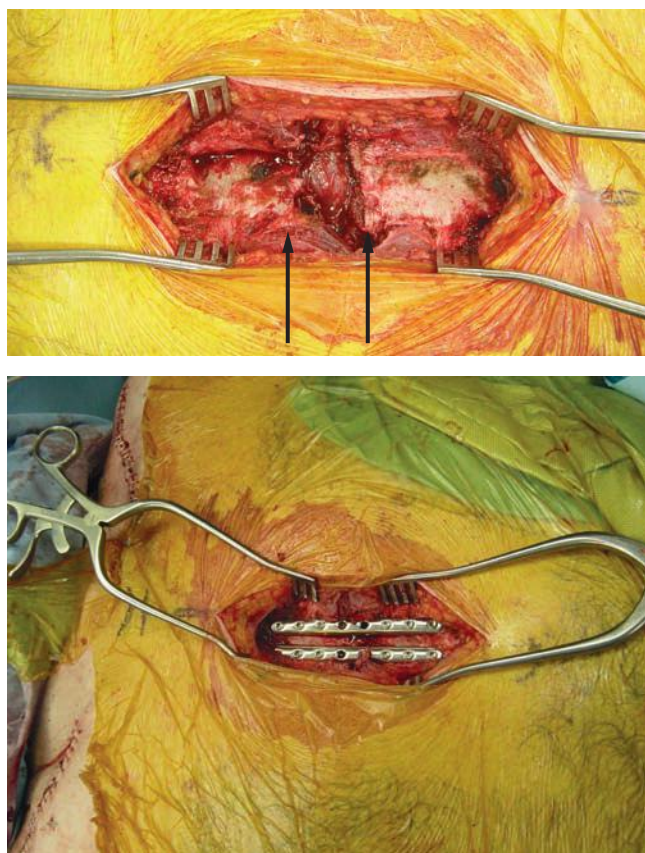


Figure 7-58. Significant sternal displacement (A; arrows) can be reduced and stabilized with sternal plating (B).

Regardless of the etiology, acute injuries are usually repaired through an abdominal approach to manage potential associated intraperitoneal visceral injury. After delineation of the injury, the chest should be evacuated of all blood and particulate matter, and thoracostomy tube placed if not previously done. Allis clamps are used to approximate the diaphragmatic edges, and the defect is closed with a running No. 1 polypropylene suture. Occasionally, large avulsions or shotgun wounds with extensive tissue loss will require polypropylene or biologic mesh to bridge the defect. Alternatively, transposition of the diaphragm cephalad one to two intercostal spaces may allow repair without undue tension.⁶¹

Abdominal Injuries

Liver and Extrahepatic Biliary Tract The liver's large size makes it the organ most susceptible to blunt trauma, and it is frequently involved in upper torso penetrating wounds. Nonoperative management of solid organ injuries is pursued in hemodynamically stable patients who do not have overt peritonitis or other indications for laparotomy. Patients with > grade II injuries should be admitted to the SICU with frequent hemodynamic monitoring, determination of hemoglobin, and abdominal examination. The only absolute contraindication to nonoperative management is hemodynamic instability. Factors such as high injury grade, large hemoperitoneum, contrast extravasation, or pseudoaneurysms may predict complications or failure of nonoperative management. Angioembolization and endoscopic retrograde cholangiopancreatography (ERCP) are useful adjuncts that can improve the success rate of nonoperative management.^{97,98} The indication for angiography to control hepatic hemorrhage is transfusion of 4 units of RBCs in 6 hours or 6 units of RBCs in 24 hours without hemodynamic instability.

In the 15% of patients for whom emergent laparotomy is mandated, the primary goal is to arrest hemorrhage. Initial control of hemorrhage is best accomplished using perihepatic packing and manual compression. With extensive injuries and major hemorrhage a Pringle maneuver should be done immediately. Intermittent release of the Pringle is helpful to attenuate hepatic cellular loss. In either case, the edges of the liver laceration should be opposed for local pressure control of bleeding. Hemorrhage from most major hepatic injuries can be controlled with effective perihepatic packing. The right costal margin is elevated, and the pads are strategically placed over and around the bleeding site (see Fig. 7-36). Additional pads should be placed between the liver, diaphragm, and anterior chest wall until the bleeding has been controlled. Sometimes 10 to 15 pads may be required to control the hemorrhage from an extensive right lobar injury. Packing of injuries of the left lobe is not as effective, because there is insufficient abdominal and thoracic wall anterior to the left lobe to provide adequate compression with the abdomen open. Fortunately, hemorrhage from the left lobe usually can be controlled by mobilizing the lobe and compressing it between the surgeon's hands. If the patient has persistent bleeding despite packing, injuries to the hepatic artery, portal vein, and retrohepatic vasculature should be considered. A Pringle maneuver can help delineate the source of hemorrhage. In fact, hemorrhage from hepatic artery and portal vein injuries will halt with the application of a vascular clamp across the portal triad; whereas, bleeding from the hepatic veins and retrohepatic vena cava will continue.

Injuries of the portal triad vasculature should be addressed immediately. In general, ligation from the celiac axis to the

level of the common hepatic artery at the gastroduodenal arterial branch is tolerated due to the extensive collaterals, but the proper hepatic artery should be repaired. The right or left hepatic artery, or in urgent situations the portal vein, may be selectively ligated; occasionally, lobar necrosis will necessitate delayed anatomic resection. If the right hepatic artery is ligated, cholecystectomy also should be performed. If the vascular injury is a stab wound with clean transection of the vessels, primary end-to-end repair is done. If the injury is destructive, temporary shunting should be performed followed by interposition reversed saphenous vein graft (RSVG). Blunt avulsions of the portal structures are particularly problematic if located at the hepatic plate, flush with the liver; hemorrhage control at the liver can be attempted with directed packing or Fogarty catheters. If the avulsion is more proximal, at the superior border of the pancreatic body or even retropancreatic, the pancreas must be transected to gain access for hemorrhage control and repair.

If massive venous hemorrhage is seen from behind the liver despite use of the Pringle maneuver, the patient likely has a hepatic vein or retrohepatic vena cava injury. If bleeding can be controlled with perihepatic packing, the packing should be left undisturbed and the patient observed in the SICU. Placement of a hepatic vein stent by interventional radiology may be considered. If bleeding continues despite repeated attempts at packing, then direct repair, with or without hepatic vascular isolation, should be attempted. Three techniques have been used to accomplish hepatic vascular isolation: (a) direct repair with suprahepatic and infrahepatic clamping of the vena cava and stapled assisted parenchymal resection;⁹⁹ (b) temporary shunting of the retrohepatic vena cava; and (c) venovenous bypass (Fig. 7-59).¹⁰⁰

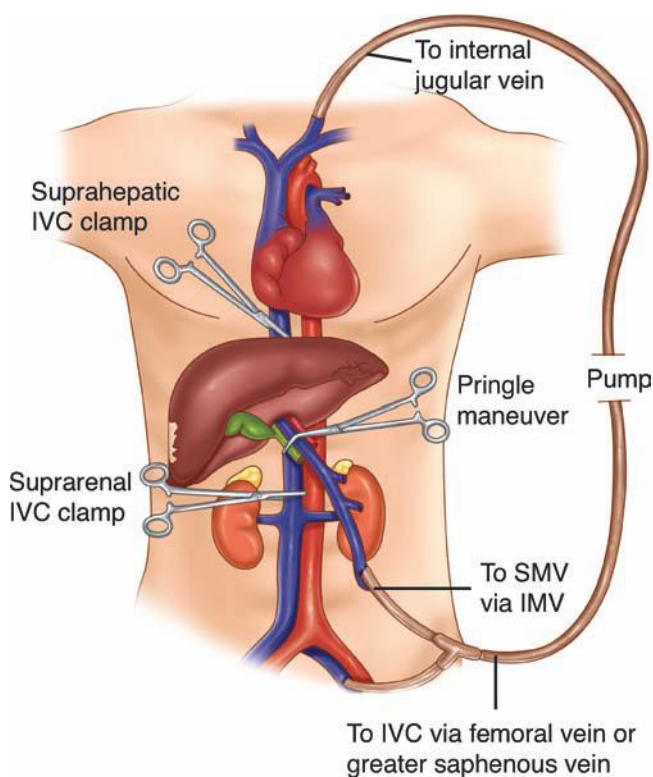


Figure 7-59. Venovenous bypass permits hepatic vascular isolation with continued venous return to the heart. IMV = inferior mesenteric vein; IVC = inferior vena cava; SMV = superior mesenteric vein.

Numerous methods for the definitive control of hepatic parenchymal hemorrhage have been developed. Minor lacerations may be controlled with manual compression applied directly to the injury site. Topical hemostatic techniques include the use of an electrocautery (with the device set at 100 watts), argon beam coagulator, microcrystalline collagen, thrombin-soaked gelatin foam sponge, fibrin glue, and BioGlue. Suturing of the hepatic parenchyma with a blunt tipped 0 chromic suture (e.g., a “liver suture”) can be an effective hemostatic technique. A running suture is used to approximate the edges of shallow lacerations, whereas deeper lacerations are approximated using interrupted horizontal mattress sutures placed parallel to the edge of the laceration. When the suture is tied, tension is adequate when visible hemorrhage ceases or the liver blanches around the suture. Caution must be used to prevent hepatic necrosis. This technique of placing large liver sutures controls bleeding through reapproximation of the liver laceration rather than direct ligation of bleeding vessels. Aggressive finger fracture to identify bleeding vessels followed by individual clip or suture ligation was advocated previously but currently has a limited role in hemostasis. Hepatic lobar arterial ligation may be appropriate for patients with recalcitrant arterial hemorrhage from deep within the liver and is a reasonable alternative to a deep hepatotomy, particularly in unstable patients. Omentum can be used to fill large defects in the liver. The tongue of omentum not only obliterates potential dead space with viable tissue but also provides an excellent source of macrophages. Additionally, the omentum can provide buttressing support for parenchymal sutures.

Translumbal penetrating injuries are particularly challenging, because the extent of the injury cannot be fully visualized. As discussed later in “Damage Control Surgery,” options include intraparenchymal tamponade with a Foley catheter or balloon occlusion (see Fig. 7-48).¹⁰¹ If tamponade is successful with either modality, the balloon is left inflated for 24 to 48 hours followed by sequential deflation and removal at a second laparotomy. Hepatotomy with ligation of individual bleeders occasionally may be required; however, division of the overlying viable hepatic tissue may cause considerable blood loss in the coagulopathic patient. Finally, angioembolization is an effective adjunct in any of these scenarios and should be considered early in the course of treatment.

Several centers have reported patients with devastating hepatic injuries or necrosis of the entire liver who have undergone successful hepatic transplantation.¹⁰² Clearly this is dramatic therapy, and the patient must have all other injuries delineated, particularly those of the central nervous system, and have an excellent chance of survival excluding the hepatic injury. Because donor availability will limit such procedures, hepatic transplantation for trauma will continue to be performed only in extraordinary circumstances.

Cholecystectomy is performed for injuries of the gallbladder and after operative ligation of the right hepatic artery. Injuries of the extrahepatic bile ducts are a challenge due to their small size and thin walls. Because of the proximity of other portal structures and the vena cava, associated vascular injuries are common. These factors may preclude primary repair. Small lacerations with no accompanying loss or devitalization of adjacent tissue can be treated by the insertion of a T tube through the wound or by lateral suturing using 6-0 monofilament absorbable suture. Virtually all transections and any injury associated with significant tissue loss will require a Roux-en-Y choledochojunostomy.¹⁰³

The anastomosis is performed using a single-layer interrupted technique with 5-0 monofilament absorbable suture. To reduce anastomotic tension, the jejunum should be sutured to the areolar tissue of the hepatic pedicle or porta hepatis. Injuries of the hepatic ducts are almost impossible to satisfactorily repair under emergent circumstances. One approach is to intubate the duct for external drainage and attempt a repair when the patient recovers or attempt stenting via ERC. Alternatively, the duct can be ligated if the opposite lobe is normal and uninjured.

Patients undergoing perihepatic packing for extensive liver injuries typically are returned to the OR for pack removal 24 hours after initial injury. Earlier exploration may be indicated in patients with evidence of ongoing hemorrhage. Signs of rebleeding are usually conspicuous, and include a falling hemoglobin, accumulation of blood clots under the temporary abdominal closure device, and bloody output from drains; the magnitude of hemorrhage is reflected in ongoing hemodynamic instability and metabolic monitoring. Postoperative hemorrhage should be re-evaluated in the OR once the patient's coagulopathy is corrected. Alternatively, angioembolization is appropriate for complex injuries. Patients with hepatic ischemia due to prolonged intraoperative use of the Pringle maneuver have an expected elevation but subsequent resolution of transaminase levels, whereas patients requiring hepatic artery ligation may have frank hepatic necrosis. Although febrile patients should be

evaluated for infectious complications, patients with complex hepatic injuries typically have intermittent "liver fever" for the first 5 days after injury.

Aside from hemorrhage and hepatic necrosis, additional complications after significant hepatic trauma include bilomas, arterial pseudoaneurysms, and biliary fistulas (Fig. 7-60). Bilomas are loculated collections of bile, which may or may not be infected. If infected, they should be treated like an abscess via percutaneous drainage. Although small, sterile bilomas eventually will be reabsorbed, larger fluid collections should be drained. Biliary ascites, due to the disruption of a major bile duct, often requires reoperation and wide drainage. Primary repair of the injured intrahepatic duct is unlikely to be successful. Resectional débridement is indicated for the removal of peripheral portions of nonviable hepatic parenchyma.

Pseudoaneurysms and biliary fistulas are rare complications in patients with hepatic injuries. Because hemorrhage from hepatic injuries often is treated without isolating individual bleeding vessels, arterial pseudoaneurysms may develop, with the potential for rupture. Rupture into a bile duct results in hemobilia, which is characterized by intermittent episodes of right upper quadrant pain, upper GI hemorrhage, and jaundice. If the aneurysm ruptures into a portal vein, portal venous hypertension with bleeding esophageal varices may occur. Either scenario is best managed with hepatic arteriography and

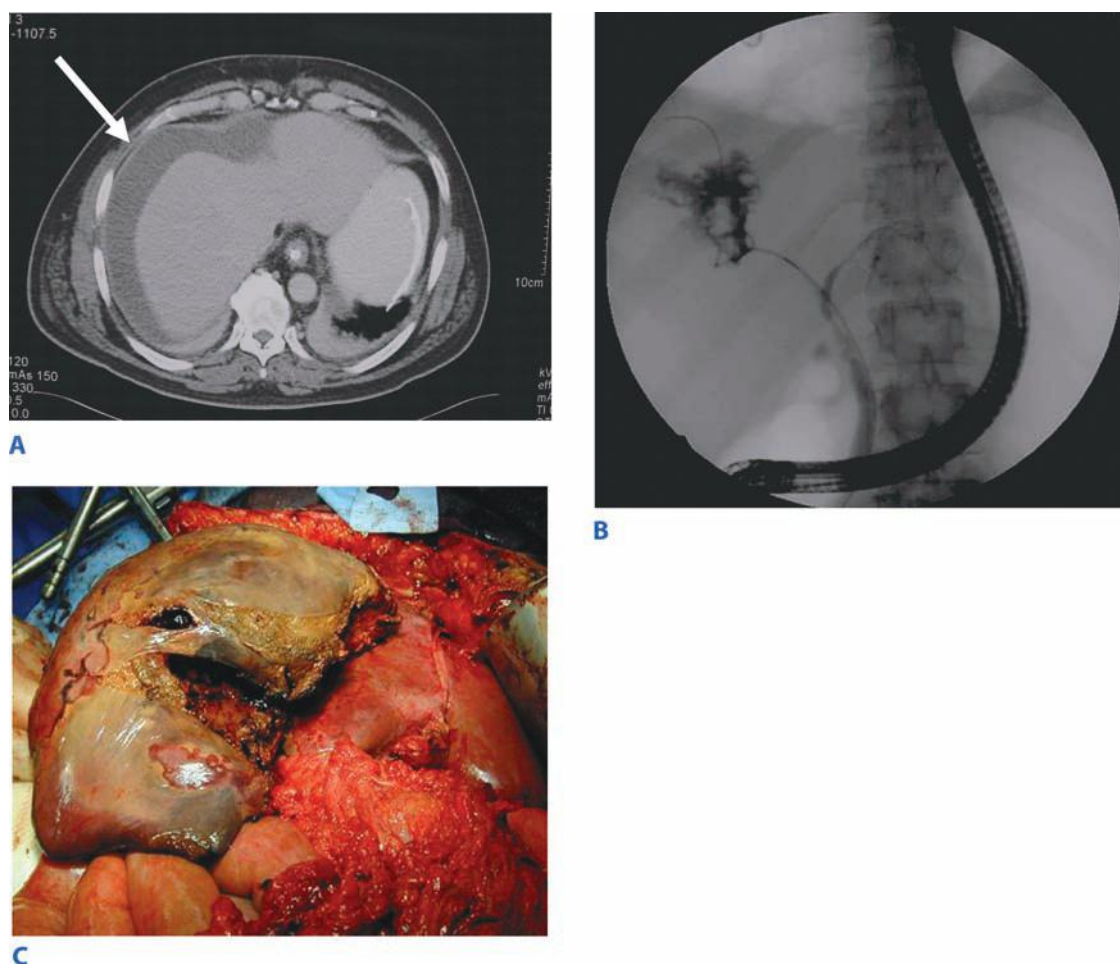


Figure 7-60. Complications after hepatic trauma include bilomas (A; arrow), hepatic duct injuries (B), and hepatic necrosis after hepatic artery ligation or embolization (C).

embolization. Biliovenous fistulas, causing jaundice due to rapid increases in serum bilirubin levels, should be treated with ERCP and sphincterotomy. Rarely, a biliary fistulous communication will form with intrathoracic structures in patients with associated diaphragm injuries, resulting in a bronchobiliary or pleurobiliary fistula. Due to the pressure differential between the biliary tract (positive) and the pleural cavity (negative), the majority require operative closure. Occasionally, endoscopic sphincterotomy with stent placement will be required to address the pressure differential, and the pleurobiliary fistula will close spontaneously.

Spleen Until the 1970s, splenectomy was considered mandatory for all splenic injuries. Recognition of the immune function of the spleen refocused efforts on operative splenic salvage in the 1980s.^{104,105} After demonstrated success in pediatric patients, however, nonoperative management has become the preferred means of splenic salvage. The identification of contrast extravasation as a risk factor for failure of nonoperative management led to liberal use of angioembolization. The role of selective angioembolization (SAE) in splenic salvage remains controversial with some groups advocating pre-emptive SAE.¹⁰⁶ It is clear, however, that up to 20% of patients with splenic trauma warrant early splenectomy and that failure of nonoperative management often represents inappropriate patient selection.^{107,108} Unlike hepatic injuries, which usually rebleed within 48 hours, delayed hemorrhage or rupture of the spleen can occur up to weeks after injury. Indications for early intervention include initiation of blood transfusion within the first 12 hours and hemodynamic instability.

Splenic injuries are managed operatively by splenectomy, partial splenectomy, or splenic repair (splenorrhaphy), based on the extent of the injury and the physiologic condition of the patient. Splenectomy is indicated for hilar injuries, pulverized splenic parenchyma, or any >grade II injury in a patient with coagulopathy or multiple injuries. The authors use autotransplantation of splenic implants (Fig. 7-61) to achieve partial immunocompetence in younger patients who do not have an associated enteric injury. Drains are not used. Partial splenectomy can be employed in patients in whom only the superior or inferior pole has been injured. Hemorrhage from the raw splenic

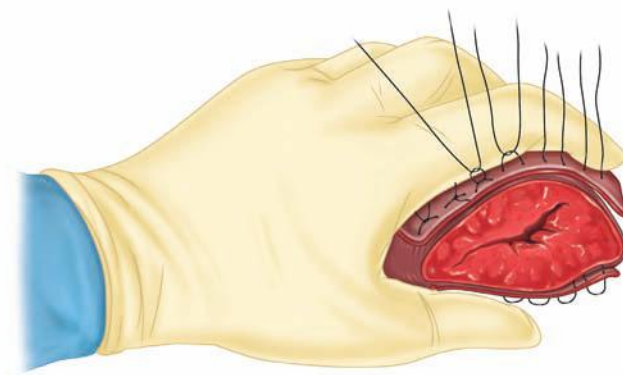


Figure 7-62. Interrupted pledgeted sutures may effectively control hemorrhage from the cut edge of the spleen.

edge is controlled with horizontal mattress sutures, with gentle compression of the parenchyma (Fig. 7-62). As with hepatic injuries, splenorrhaphy hemostasis is achieved by topical methods (electrocautery; argon beam coagulation; application of thrombin-soaked gelatin foam sponges, fibrin glue, or BioGlue), envelopment of the injured spleen in absorbable mesh, and pledgeted suture repair.

After splenectomy or splenorrhaphy, postoperative hemorrhage may be due to loosening of a tie around the splenic vessels, an improperly ligated or unrecognized short gastric artery, or recurrent bleeding from the spleen if splenic repair was used. An immediate postsplenectomy increase in platelets and WBCs is normal; however, beyond postoperative day 5, a WBC count above 15,000/mm³ and a platelet/WBC ratio of <20 are strongly associated with sepsis and should prompt a thorough search for underlying infection.¹⁰⁹ A common infectious complication after splenectomy is a subphrenic abscess, which should be managed with percutaneous drainage. Additional sources of morbidity include a concurrent but unrecognized iatrogenic injury to the pancreatic tail during rapid splenectomy resulting in pancreatic ascites or fistula, and a gastric perforation during short gastric ligation. Enthusiasm for splenic salvage was driven by the rare, but often fatal, complication of overwhelming postsplenectomy

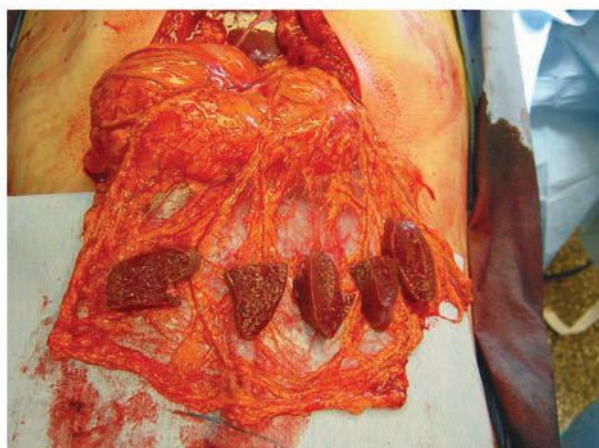
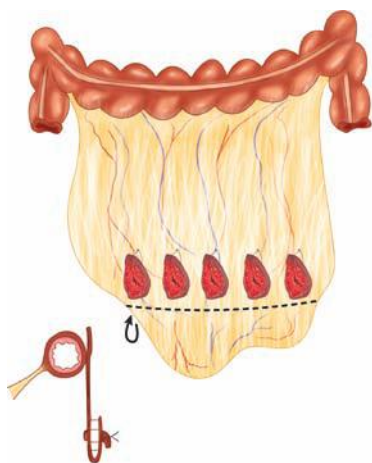


Figure 7-61. Autologous splenic transplantation is performed by placing sections of splenic parenchyma, 40 × 40 × 3 mm in size, into pouches in the greater omentum.

sepsis. Overwhelming postsplenectomy sepsis is caused by encapsulated bacteria, *Streptococcus pneumoniae*, *Haemophilus influenzae*, and *Neisseria meningitidis*, which are resistant to antimicrobial treatment. In patients undergoing splenectomy, prophylaxis against these bacteria is provided via vaccines administered optimally at 14 days.¹¹⁰

Stomach and Small Intestine Little controversy exists regarding the repair of injuries to the stomach or small bowel because of a rich blood supply. Gastric wounds can be oversewn with a running single-layer suture line or closed with a stapler. If a single-layer closure is chosen, full-thickness bites should be taken to ensure hemostasis from the well-vascularized gastric wall. The most commonly missed gastric injury is the posterior wound of a totally penetrating injury. Injuries also can be overlooked if the wound is located within the mesentery of the lesser curvature or high in the posterior fundus. To delineate a questionable injury, the stomach can be digitally occluded at the pylorus while methylene blue-colored saline is instilled via a nasogastric tube. Alternatively, air can be introduced via the NG tube with the abdomen filled with saline. Partial gastrectomy may be required for destructive injuries, with resections of the distal antrum or pylorus reconstructed using a Billroth procedure. Patients with injuries that damage both Latarjet nerves or vagi should undergo a drainage procedure (see Chap. 26). Small intestine injuries can be repaired using a transverse running 3-0 PDS suture if the injury is less than one-third the circumference of the bowel. Destructive injuries or multiple penetrating injuries occurring close together are treated with segmental resection followed by end-to-end anastomosis using a continuous, single-layer 3-0 polypropylene suture.¹¹¹ Mesenteric injuries may result in an ischemic segment of intestine, which mandates resection.

Following repair of GI tract injuries, there is an obligatory postoperative ileus. Return of bowel function is indicated by a decrease in gastrostomy or nasogastric tube output. The topic of nutrition is well covered in other chapters, but a few issues warrant mention. Multiple studies have confirmed the importance of early total enteral nutrition (TEN) in the trauma population, particularly its impact in reducing septic complications.¹¹² The route of enteral feedings (stomach vs. small bowel) tends to be less important, because gut tolerance appears equivalent unless there is upper GI tract pathology. Although early enteral nutrition is the goal, evidence of bowel function should be apparent before advancing to goal tube feedings. Overzealous jejunal feeding can lead to small bowel necrosis in the patient recovering from profound shock. Patients undergoing monitoring for nonoperative management of grade II or higher solid organ injuries should receive nothing by mouth for at least 48 hours in case they require an operation. Although there is general reluctance to initiate TEN in patients with an open abdomen, a recent multicenter trial demonstrates TEN in the postinjury open abdomen is feasible.¹¹³ For those patients without a bowel injury, TEN was associated with higher fascial closure rates, decreased complications, and decreased mortality. TEN in patients with bowel injuries does not appear to alter fascial closure rates, complications, or mortality; hence EN appears to be neither advantageous nor detrimental in these patients. Prospective randomized controlled trials are warranted to further clarify the role of EN in this subgroup. Once resuscitation is complete, initiation of TEN, even at trophic levels (20 mL/h), should be considered in all injured patients with an open abdomen.

Duodenum and Pancreas The spectrum of injuries to the duodenum includes hematomas, perforation (blunt blow-outs, lacerations from stab wounds, or blast injury from gunshot wounds), and combined pancreaticoduodenal injuries. The majority of duodenal hematomas are managed nonoperatively with nasogastric suction and parenteral nutrition. Patients with suspected associated perforation, suggested by clinical deterioration or imaging with retroperitoneal free air or contrast extravasation, should undergo operative exploration. A marked drop in nasogastric tube output heralds resolution of the hematoma, which typically occurs within 2 weeks; repeat imaging to confirm these clinical findings is optional. If the patient shows no clinical or radiographic improvement within 3 weeks, operative evaluation is warranted.

Small duodenal perforations or lacerations should be treated by primary repair using a running single-layer suture of 3-0 monofilament. The wound should be closed in a direction that results in the largest residual lumen. Challenges arise when there is a substantial loss of duodenal tissue. Extensive injuries of the first portion of the duodenum (proximal to the duct of Santorini) can be repaired by débridement and end-to-end anastomosis because of the mobility and rich blood supply of the distal gastric atrium and pylorus. In contrast, the second portion is tethered to the head of the pancreas by its blood supply and the ducts of Wirsung and Santorini; therefore, no more than 1 cm of duodenum can be mobilized away from the pancreas, and this does not effectively alleviate tension on the suture line. Moreover, suture repair using an end-to-end anastomosis in the second portion often results in an unacceptably narrow lumen. Therefore, defects in the second portion of the duodenum should be patched with a vascularized jejunal graft. Duodenal injuries with tissue loss distal to the papilla of Vater and proximal to the superior mesenteric vessels are best treated by Roux-en-Y duodenojejunostomy with the distal portion of the duodenum oversewn (Fig. 7-63). In particular, injuries in the distal third and fourth portions of the duodenum (behind the mesenteric vessels) should be resected, and a duodenojejunostomy performed on the left side of the superior mesenteric vessels.

Optimal management of pancreatic trauma is determined by where the parenchymal damage is located and whether the intrapancreatic common bile duct and main pancreatic duct remain intact. Patients with pancreatic contusions (defined as injuries that leave the ductal system intact) can be treated nonoperatively or with closed suction drainage if undergoing laparotomy for other indications. Patients with proximal pancreatic injuries, defined as those that lie to the right of the superior mesenteric vessels, are also managed with closed suction drainage.¹¹⁴ In contrast, distal pancreatic injuries are managed based upon ductal integrity. Pancreatic duct disruption can be identified through direct exploration of the parenchymal laceration, operative pancreatography, ERCP, or magnetic resonance cholangiopancreatography. Patients with distal ductal disruption undergo distal pancreatectomy, preferably with splenic preservation.

Injuries to the pancreatic head add an additional element of complexity because the intrapancreatic portion of the common bile duct traverses this area and often converges with the pancreatic duct. In contrast to diagnosis of pancreatic duct injuries, identification of intrapancreatic common bile duct disruption is relatively simple. The first method is to squeeze the gallbladder and look for bile leaking from the pancreatic wound. Otherwise,

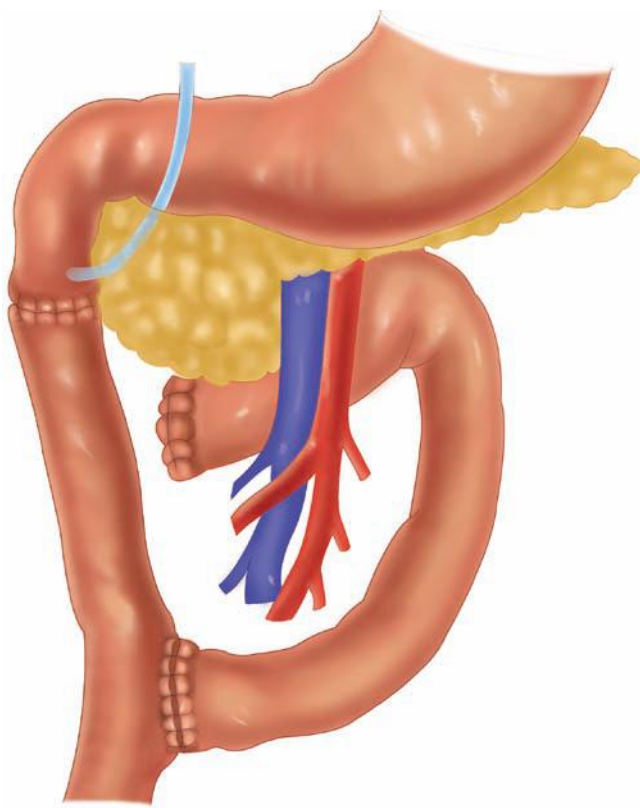


Figure 7-63. Roux-en-Y duodenojejunostomy is used to treat duodenal injuries between the papilla of Vater and superior mesenteric vessels when tissue loss precludes primary repair.

cholangiography, optimally via the cystic duct, is diagnostic. Definitive treatment of this injury entails division of the common bile duct superior to the first portion of the duodenum, with ligation of the distal duct and reconstruction with a Roux-en-Y choledochojejunostomy. For injuries to the head of the pancreas that involve the main pancreatic duct but not the intrapancreatic bile duct, there are few options. Distal pancreatectomy alone is rarely indicated due to the extended resection of normal gland and the resultant risk of pancreatic insufficiency. Central pancreatectomy preserves the common bile duct, and mobilization of the pancreatic body permits drainage into a Roux-en-Y pancreaticojejunostomy (Fig. 7-64). Although this approach avoids a pancreaticoduodenectomy (Whipple procedure), the complexity may make the pancreaticoduodenectomy more appropriate in patients with multiple injuries. Some injuries of the pancreatic head do not involve either the pancreatic or common bile duct; if no clear ductal injury is present, drains are placed. Rarely, patients sustain destructive injuries to the head of the pancreas or combined pancreaticoduodenal injuries that require pancreaticoduodenectomy. Examples of such injuries include transection of both the intrapancreatic bile duct and the main pancreatic duct in the head of the pancreas, avulsion of the papilla of Vater from the duodenum, and destruction of the entire second portion of the duodenum. In these cases of extensive injuries, damage control principles are often employed.

In contrast to proximal injuries, pancreatic resection continues to be advocated for major ductal disruption in the more distal pancreas. Several options exist for treating injuries of the pancreatic body and tail. In stable patients, spleen-preserving distal pancreatectomy should be performed. An alternative,

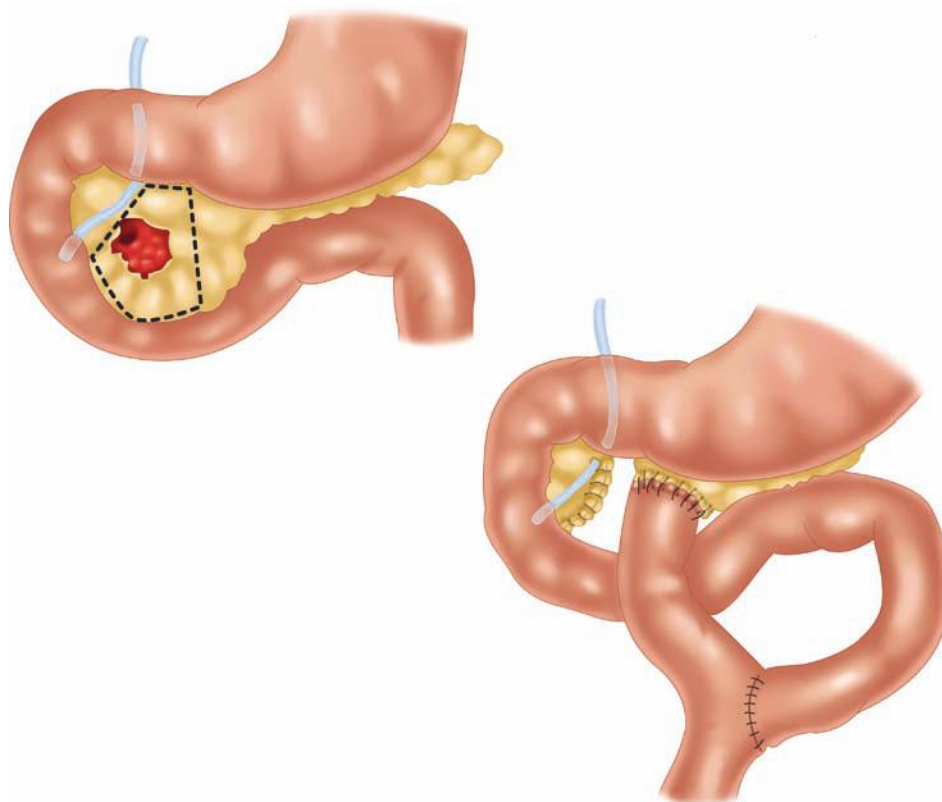


Figure 7-64. For injuries of the pancreatic head that involve the pancreatic duct but spare the common bile duct, central pancreatic resection with Roux-en-Y pancreaticojejunostomy prevents pancreatic insufficiency.

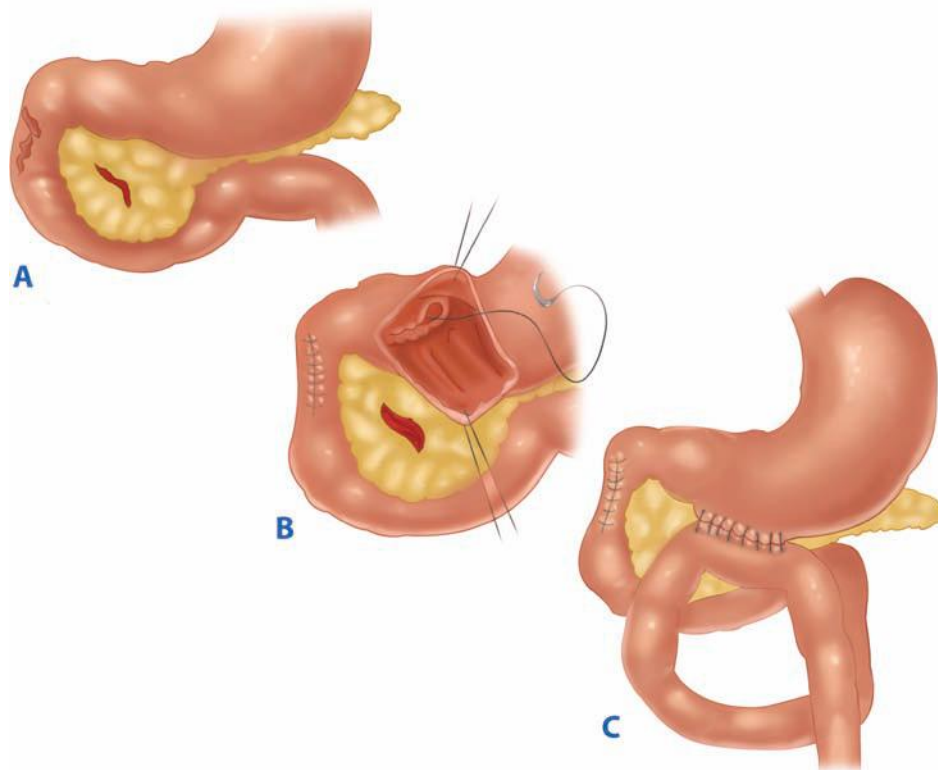


Figure 7-65. A. Pyloric exclusion is used to treat combined injuries of the duodenum and the head of the pancreas as well as isolated duodenal injuries when the duodenal repair is less than optimal. B and C. The pylorus is oversewn through a gastrotomy, which is subsequently used to create a gastrojejunostomy. The authors frequently use needle-catheter jejunostomy tube feedings for these patients.

which preserves both the spleen and distal transected end of the pancreas, is either a Roux-en-Y pancreaticojejunostomy or pancreaticogastrostomy. If the patient is physiologically compromised, distal pancreatectomy with splenectomy is the preferred approach. Regardless of the choice of definitive procedure, the pancreatic duct in the proximal edge of transected pancreas should be individually ligated or occluded with a TA stapler. Application of fibrin glue over the stump may be advantageous.

Pyloric exclusion often is used to divert the GI stream after high-risk, complex duodenal repairs (Fig. 7-65).¹¹⁵ If the duodenal repair breaks down, the resultant fistula is an end fistula, which is easier to manage and more likely to close than a lateral fistula. To perform a pyloric exclusion, first a gastrotomy is made on the greater curvature near the pylorus. The pylorus is then grasped with a Babcock clamp, via the gastrotomy, and oversewn with an O polypropylene suture. A gastrojejunostomy restores GI tract continuity. Vagotomy is not necessary because a risk of marginal ulceration has not been documented. Perhaps surprisingly, the sutures maintain diversion for only 3 to 4 weeks. Alternatively, the most durable pyloric closure is a double external staple line across the pylorus using a TA stapler.

Complications should be expected after major pancreaticoduodenal injuries. Delayed hemorrhage is rare but may occur with pancreatic necrosis or abdominal infection; this usually can be managed by angioembolization. If closed suction drains have been inserted for major pancreatic trauma, these should remain in place until the patient is tolerating an oral diet or enteral nutrition. Pancreatic fistula is diagnosed after postoperative day 5 in patients with drain output of >30 mL/d and a drain amylase

level three times the serum value. Pancreatic fistula develops in over 20% of patients with combined injuries and should be managed similar to fistulas after elective surgery (see Chap. 33). Similarly, a duodenal fistula, presumptively an end fistula if a pyloric exclusion has been done, will typically heal in 6 to 8 weeks with adequate drainage and control of intra-abdominal sepsis. Pancreatic pseudocysts in patients managed nonoperatively suggest a missed injury, and ERCP should be done to evaluate the integrity of the pancreatic duct. Late pseudocysts may be a complication of operative management and are treated much like those in patients with pancreatitis (see Chap. 33). Intra-abdominal abscesses are common and routinely managed with percutaneous drainage.

Colon and Rectum Currently, three methods for treating colonic injuries are used: primary repair, end colostomy, and primary repair with diverting ileostomy. Primary repairs include lateral suture repair or resection of the damaged segment with reconstruction by ileocolostomy or colocolostomy. All suturing and anastomoses are performed using a running single-layer technique (Fig. 7-66).¹¹¹ The advantage of definitive treatment must be balanced against the possibility of anastomotic leakage if suture lines are created under suboptimal conditions. Alternatively, although use of an end colostomy requires a second operation, an unprotected suture line with the potential for breakdown is avoided. Numerous large retrospective and several prospective studies have now clearly demonstrated that primary repair is safe and effective in virtually all patients with penetrating wounds.¹¹⁶ Colostomy is still appropriate in a

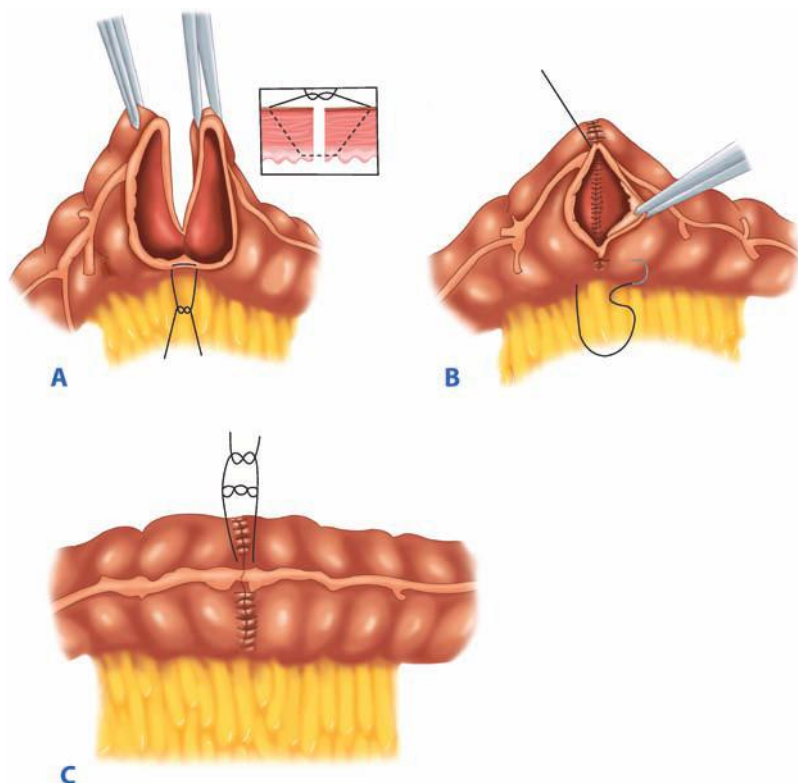


Figure 7-66. Technique for bowel repair and anastomosis. **A.** The running, single-layer suture is started at the mesenteric border. **B.** Stitches are spaced 3 to 4 mm from the edge of the bowel and advanced 3 to 4 mm, including all layers except the mucosa. **C.** The continuous suture is tied near the antimesenteric border.

few patients, but the current dilemma is how to select which patients should undergo the procedure. Currently, the overall physiologic status of the patient, rather than local factors, directs decision making. Patients with devastating left colon injuries requiring damage control are clearly candidates for temporary colostomy. Diverting ileostomy with colocolostomy, however, is used for most other high-risk patients.

Rectal injuries are similar to colonic injuries with respect to the ecology of the luminal contents, overall structure, and blood supply of the wall, but access to extraperitoneal injuries is limited due to the surrounding bony pelvis. Therefore, indirect treatment with intestinal diversion usually is required. The current options are loop ileostomy and sigmoid loop colostomy. These are preferred because they are quick and easy to perform, and provide essentially total fecal diversion. For sigmoid colostomy, technical elements include: (a) adequate mobilization of the sigmoid colon so that the loop will rest on the abdominal wall without tension, (b) maintenance of the spur of the colostomy (the common wall of the proximal and distal limbs after maturation) above the level of the skin with a one-half-inch nylon rod or similar device, (c) longitudinal incision in the tenia coli, and (d) immediate maturation in the OR (Fig. 7-67). If the injury is accessible (e.g., in the posterior intraperitoneal portion of the rectum), repair of the injury should also be attempted. However, it is not necessary to explore the extraperitoneal rectum to repair a distal perforation. If the rectal injury is extensive, another option is to divide the rectum at the level of the injury, oversew or staple the distal rectal pouch if possible, and create an end colostomy (Hartmann's procedure). Extensive injuries may warrant presacral drainage with Penrose drains placed along Waldeyer's fascia via a perianal incision (see Fig. 7-67). In rare instances in which destructive injuries are present, an abdominoperineal resection may be necessary to avert lethal pelvic sepsis.

Complications related to colorectal injuries include intra-abdominal abscess, fecal fistula, wound infection, and stomal complications. Intra-abdominal abscesses occur in approximately 10% of patients, and most are managed with percutaneous drainage. Fistulas occur in 1% to 3% of patients and usually present as an abscess or wound infection with subsequent continuous drainage of fecal output; the majority will heal spontaneously with routine care (see Chap. 29). Stomal complications (necrosis, stenosis, obstruction, and prolapse) occur in 5% of patients and may require either immediate or delayed reoperation. Stomal necrosis should be carefully monitored, because spread beyond the mucosa may result in septic complications, including necrotizing fasciitis of the abdominal wall. Penetrating injuries that involve both the rectum and adjacent bony structures are prone to development of osteomyelitis. Bone biopsy is performed for diagnosis and bacteriologic analysis, and treatment entails long-term IV antibiotic therapy and occasionally débridement.

Abdominal and Pelvic Vasculature Injury to the major arteries and veins in the abdomen can be a technical challenge.^{117–121} Although penetrating trauma indiscriminately affects all blood vessels, blunt trauma most commonly involves renal vasculature and occasionally the abdominal aorta. Patients with a penetrating aortic wound who survive to reach the OR frequently have a contained hematoma within the retroperitoneum. Due to lack of mobility of the abdominal aorta, few injuries are amenable to primary repair. Small lateral perforations may be controlled with 4-0 polypropylene suture or a PTFE patch, but end-to-end interposition grafting with a PTFE tube graft is the most common repair. Blunt injuries are typically extensive intimal tears of the infrarenal aorta and are exposed via a direct approach; most require an interposition graft. To avoid future vascular-enteric fistulas, the vascular suture lines should be covered with omentum.

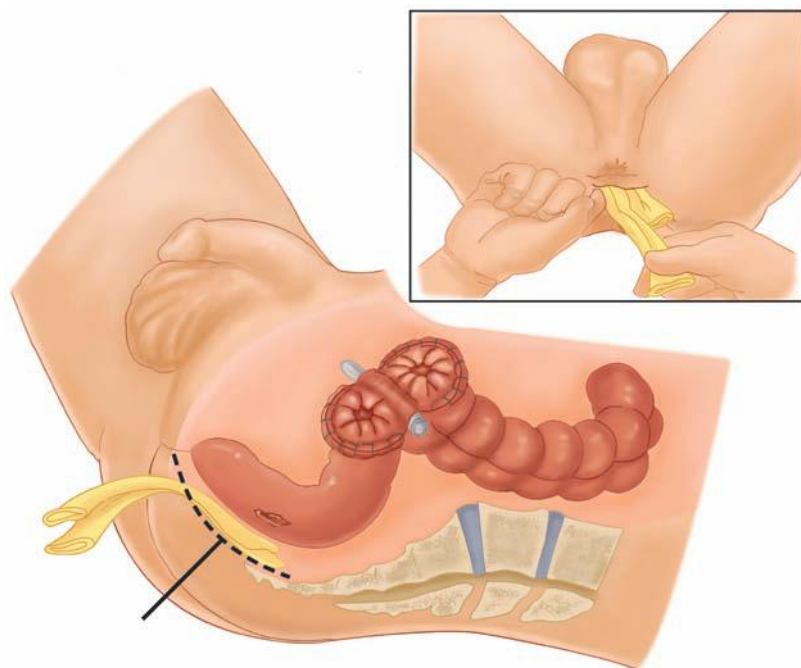


Figure 7-67. Loop colostomy will completely divert the fecal flow, allowing the low rectal injury to heal. For extensive wounds, presacral drains are inserted through a perianal incision (*box*) and advanced along Waldeyer's fascia (*dashed line*).

Penetrating wounds to the superior mesenteric artery (SMA) are typically encountered upon exploration for a gunshot wound, with “black bowel” and associated supramesocolic hematoma being pathognomonic. Blunt avulsions of the SMA are rare but should be considered in patients with a seat belt sign who have midepigastria pain or tenderness and associated hypotension. For injuries of the SMA, temporary damage control with a Pruitt-Inahara shunt can prevent extensive bowel necrosis; additionally, temporary shunting allows control of visceral contamination before placement of a PTFE graft. For definitive repair, end-to-end interposition RSVG from the proximal SMA to the SMA past the point of injury can be performed if there is no associated pancreatic injury. Alternatively, if the patient has an associated pancreatic injury, the graft should be tunneled from the distal aorta beneath the duodenum to the distal SMA. For proximal SMV injuries, digital compression for hemorrhage control is followed by attempted venorrhaphy; ligation is an option in a life-threatening situation, but the resultant bowel edema requires aggressive fluid resuscitation. Temporary abdominal closure and a second-look operation to evaluate bowel viability should be done.

Transpelvic gunshot wounds or blunt injuries with associated pelvic fractures are the most common scenarios in patients with iliac artery injuries. As with abdominal vascular injuries, a Pruitt-Inahara shunt can be used for temporary shunting of the vessel for damage control. Definitive interposition grafting with excision of the injured segment is appropriate (see “Vascular Repair Techniques”). Careful monitoring for distal embolic events and reperfusion injury necessitating fasciotomy is imperative.

In general, outcome after pelvic vascular injuries is related to (a) the technical success of the vascular reconstruction and (b) associated soft tissue and nerve injuries. Vascular repairs rarely fail after the first 12 hours, whereas, soft tissue infection is a limb threat for several weeks. Following aortic interposition grafting, the patient's SBP should not exceed 120 mm Hg for at least the first 72 hours postoperatively. Patients requiring

ligation of an inferior vena cava injury often develop marked bilateral lower extremity edema. To limit the associated morbidity the patient's legs should be wrapped with elastic bandages from the toes to the hips and elevated at a 45- to 60-degree angle. For superior mesenteric vein injuries, either ligation or thrombosis after venorrhaphy results in marked bowel edema; fluid resuscitation should be aggressive and abdominal pressure monitoring routine in these patients. Prosthetic graft infections are rare complications, but prevention of bacteremia is imperative⁶⁷; administration of antibiotics perioperatively and treatment of secondary infections is indicated. Long-term arterial graft complications such as stenosis or pseudoaneurysms are uncommon, and routine graft surveillance rarely is performed. Consequently, long-term administration of antiplatelet agents or antithrombotics is not routine.

Genitourinary Tract When undergoing laparotomy for trauma, the best policy is to explore all penetrating wounds to the kidneys.¹²² Parenchymal renal injuries are treated with hemostatic and reconstructive techniques similar to those used for injuries of the liver and spleen: topical methods (electrocautery; argon beam coagulation; application of thrombin-soaked gelatin foam sponge, fibrin glue, or BioGlue) and pledgeted suture repair. Two caveats are recognized, however: The collecting system should be closed separately, and the renal capsule should be preserved to close over the repair of the collecting system (Fig. 7-68). Renal vascular injuries are common after penetrating trauma and may be deceptively tamponaded, which results in delayed hemorrhage. Arterial reconstruction using graft interposition should be attempted for renal preservation. For destructive parenchymal or irreparable renovascular injuries, nephrectomy may be the only option; a normal contralateral kidney must be palpated, because unilateral renal agenesis occurs in 0.1% of patients.

Over 90% of blunt renal injuries are treated nonoperatively. Hematuria typically resolves within a few days with bed rest, although rarely bleeding is so persistent that bladder

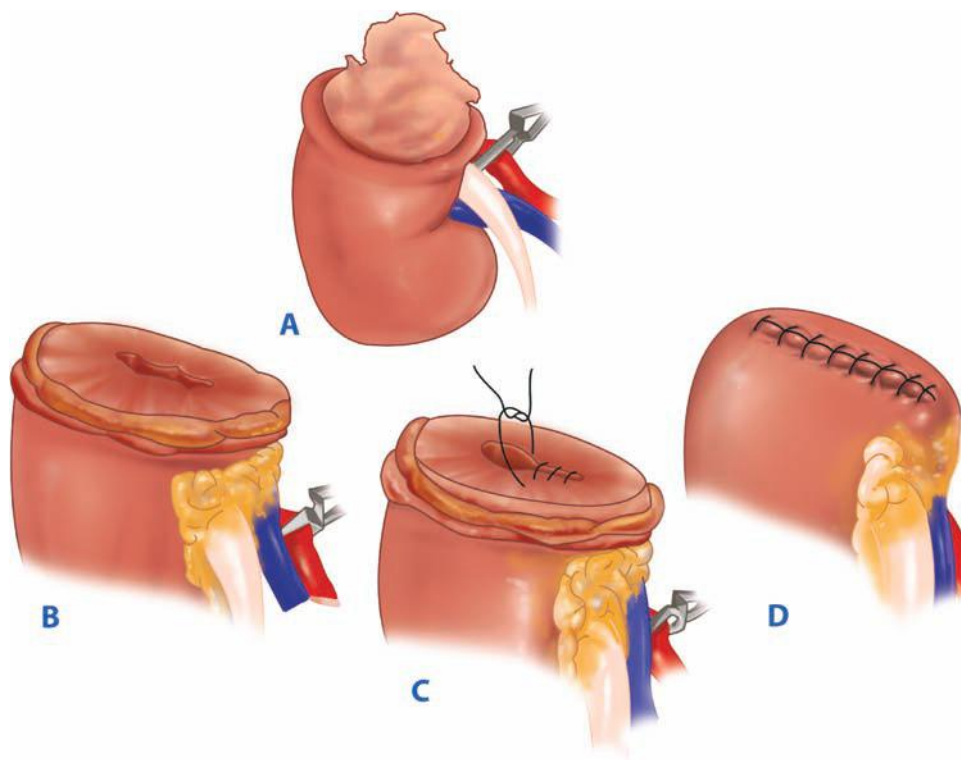


Figure 7-68. When renorrhaphy is undertaken, effective repair is assisted by attention to several key points: **A.** Vascular occlusion controls bleeding and permits adequate visualization. **B.** The renal capsule is carefully preserved. **C.** The collecting system is closed separately with absorbable suture. **D.** The preserved capsule is closed over the collecting system repair.

irrigation to dispel blood clots is warranted. Persistent gross hematuria may require embolization, whereas urinomas can be drained percutaneously. Operative intervention after blunt trauma is limited to renovascular injuries and destructive parenchymal injuries that result in hypotension. The renal arteries and veins are uniquely susceptible to traction injury caused by blunt trauma. As the artery is stretched, the inelastic intima and media may rupture, which causes thrombus formation and resultant stenosis or occlusion. The success rate for renal artery repair approaches 0%, but an attempt is reasonable if the injury is <5 hours old or if the patient has a solitary kidney or bilateral injuries.¹²³ Image-guided endostent placement is now employed for many of these injuries recognized by CT scanning. Reconstruction after blunt renal injuries may be difficult, however, because the injury is typically at the level of the aorta. If repair is not possible within this time frame, leaving the kidney in situ does not necessarily lead to hypertension or abscess formation. The renal vein may be torn or completely avulsed from the vena cava due to blunt trauma. Typically, the large hematoma causes hypotension, which leads to operative intervention. During laparotomy for blunt trauma, expanding or pulsatile perinephric hematomas should be explored. If necessary, emergent vascular control can be obtained by placing a curved vascular clamp across the hilum from an inferior approach. Techniques of repair and hemostasis are similar to those described earlier.

Injuries to the ureters are uncommon but may occur in patients with pelvic fractures and penetrating trauma. An injury may not be identified until a complication (i.e., a urinoma) becomes apparent. If an injury is suspected during operative exploration but is not clearly identified, methylene blue or indigo carmine is administered IV with observation for extravasation. Injuries are repaired using 5-0 absorbable monofilament, and mobilization of the kidney may reduce

tension on the anastomosis. Distal ureteral injuries can be treated by reimplantation facilitated with a psoas hitch and/or Boari flap. In damage control circumstances, the ureter can be ligated on both sides of the injury and a nephrostomy tube placed.

Bladder injuries are subdivided into those with intraperitoneal extravasation and those with extraperitoneal extravasation. Ruptures or lacerations of the intraperitoneal bladder are operatively closed with a running, single-layer, 3-0 absorbable monofilament suture. Laparoscopic repair is becoming common in patients not requiring laparotomy for other injuries. Extraperitoneal ruptures are treated nonoperatively with bladder decompression for 2 weeks. Urethral injuries are managed by bridging the defect with a Foley catheter, with or without direct suture repair. Strictures are not uncommon but can be managed electively.

Female Reproductive Tract Gynecologic injuries are rare. Occasionally the vaginal wall will be lacerated by a bone fragment from a pelvic fracture. Although repair is not mandated, it should be performed if physiologically feasible. More important, however, is recognition of the open fracture, need for possible drainage, and potential for pelvic sepsis. Penetrating injuries to the vagina, uterus, fallopian tubes, and ovaries are also uncommon, and routine hemostatic techniques are used. Repair of a transected fallopian tube can be attempted but probably is unjustified, because a suboptimal repair will increase the risk of tubal pregnancy. Transection at the injury site with proximal ligation and distal salpingectomy is a more prudent approach.

Pelvic Fracture Hemorrhage Control

Patients with pelvic fractures who are hemodynamically unstable are a diagnostic and therapeutic challenge for the trauma team. These injuries often occur in conjunction with other life-threatening injuries, and there is no universal agreement

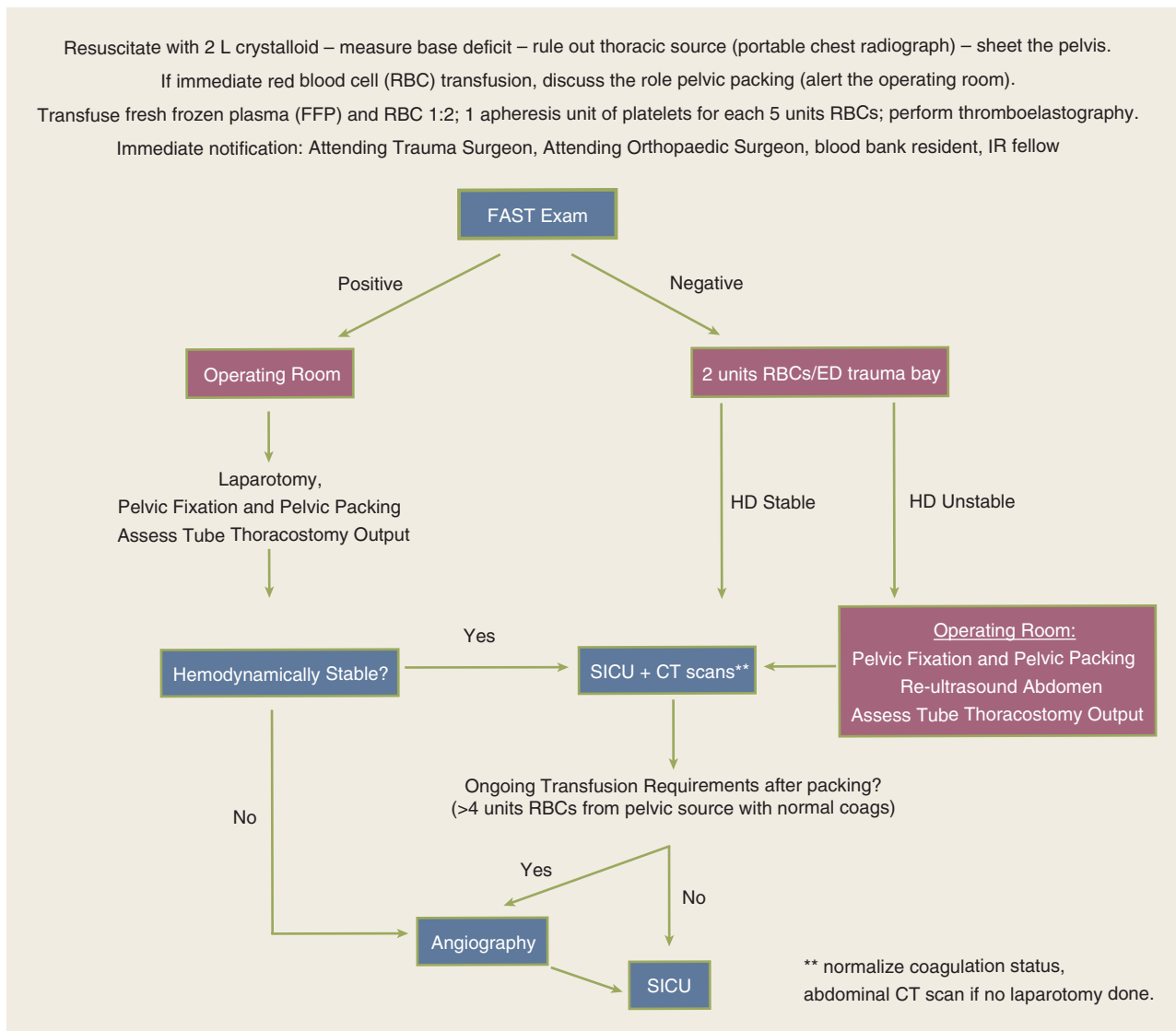


Figure 7-69. Management algorithm for patients with pelvic fractures with hemodynamic instability. CT = computed tomography; ED = emergency department; FAST = focused abdominal sonography for trauma; HD = hemodynamic; PLT = platelets; PRBCs = packed red blood cells; SICU = surgical intensive care unit.

among clinicians on management. Current management algorithms in the United States incorporate variable time frames for bony stabilization and fixation, as well as hemorrhage control by preperitoneal pelvic packing and/or angioembolization. Early institution of a multidisciplinary approach with the involvement of trauma surgeons, orthopedic surgeons, interventional radiologists, the director of the blood bank, and anesthesiologists is imperative due to high associated mortality rates (Fig. 7-69).

Evaluation in the ED focuses on identification of injuries mandating operative intervention (e.g., massive hemothorax, ruptured spleen) and injuries related to pelvic fracture that alter management (e.g., injuries to the iliac artery). Immediate temporary stabilization with sheeting of the pelvis or application of commercially available compression devices should be performed. In high risk patients, (e.g. autopedestrian accident) with profound shock, this should be done before radiographic confirmation. If the patient's primary source of bleeding is the fracture-related hematoma, several options exist for hemorrhage control.

Because 85% of bleeding due to pelvic fractures is venous or bony in origin the authors advocate immediate external fixation and preperitoneal pelvic packing.^{124,125} Anterior external fixation decreases pelvic volume, which promotes tamponade of venous bleeding and prevents secondary hemorrhage from the shifting of bony elements. Pelvic packing, in which six laparotomy pads (four in children) are placed directly into the paravesical space through a small suprapubic incision, provides tamponade for the bleeding (Fig. 7-70). Pelvic packing also eliminates the often difficult decision by the trauma surgeon: OR vs. interventional radiology? All patients can be rapidly transported to the OR and packing can be accomplished in under 30 minutes. In the authors' experience, this results in hemodynamic stability and abrupt cessation of the need for ongoing blood transfusion in the majority of cases.¹²⁵ Patients also can undergo additional procedures such as laparotomy, thoracotomy, external fixation of extremity fractures, open fracture débridement, or craniotomy. Currently, angiography is reserved for patients with evidence of

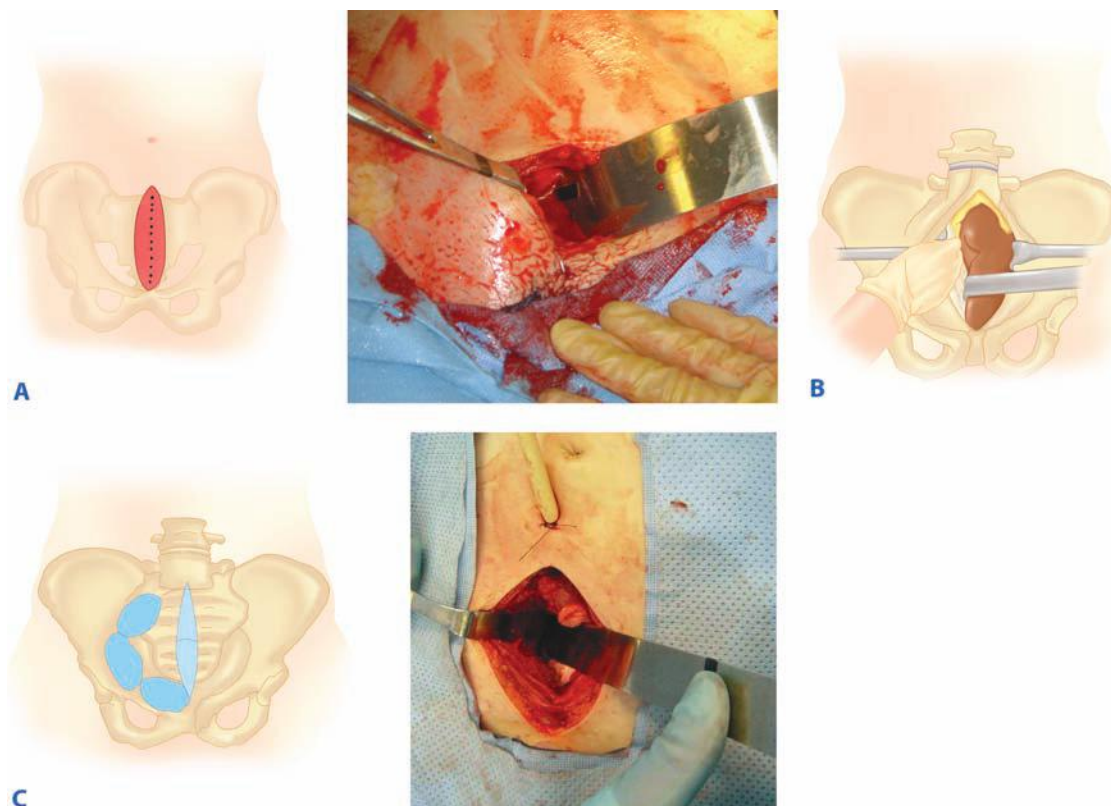


Figure 7-70. **A.** Pelvic packing is performed through a 6- to 8-cm midline incision made from the pubic symphysis cephalad, with division of the midline fascia. **B.** The pelvic hematoma often dissects the preperitoneal and paravesical space down to the presacral region, which facilitates packing; alternatively, blunt digital dissection opens the preperitoneal space for packing. **C.** Three standard surgical laparotomy pads are placed on each side of the bladder, deep within the preperitoneal space; the fascia is closed with an O polydioxanone monofilament suture and the skin with staples.

ongoing pelvic bleeding after admission to the SICU (>4 units of RBCs in the first 12 postoperative hours after the coagulopathy is corrected). Patients undergo standard posttrauma resuscitative SICU care, and the pelvic packs are removed within 48 hours, a time frame chosen empirically based on the authors' experience with liver packing. The authors elect to repack the patient's pelvis if there is persistent oozing and perform serial washouts of the preperitoneal space if it appears infected.

Another clinical challenge is the open pelvic fracture. In many instances the wounds are located in the perineum, and the risk of pelvic sepsis and osteomyelitis is high. To reduce the risk of infection, performance of a diverting sigmoid colostomy is recommended. The pelvic wound is manually débrided and then irrigated daily with a high-pressure pulsatile irrigation system until granulation tissue covers the wound. The wound is then left to heal by secondary intention with a wound vacuum-assisted wound closure (VAC) device.

Extremity Vascular Injuries, Fractures, and Compartment Syndromes

Patients with injured extremities often require a multidisciplinary approach with involvement of trauma, orthopedic, and plastic surgeons to address vascular injuries, fractures, soft tissue injuries, and compartment syndromes. Immediate stabilization of fractures or unstable joints is done in the ED using Hare traction, knee immobilizers, or plaster splints. In patients with open fractures the wound should be covered with povidone iodine (Betadine)-soaked gauze and antibiotics administered.

Options for fracture fixation include external fixation or open reduction and internal fixation with plates or intramedullary nails. Vascular injuries, either isolated or in combination with fractures, require emergent repair. Common combined injuries include clavicle/first rib fractures and subclavian artery injuries, dislocated shoulder/proximal humeral fractures and axillary artery injuries, supracondylar fractures/elbow dislocations and brachial artery injuries, femur fracture and superficial femoral artery injuries, and knee dislocation and popliteal vessel injuries. On-table angiography in the OR facilitates rapid intervention and is warranted in patients with evidence of limb threat at ED arrival. Arterial access for on-table lower extremity angiography can be obtained percutaneously at the femoral vessels with a standard arterial catheter, via femoral vessel exposure and direct cannulation, or with superficial femoral artery (SFA) exposure just above the medial knee. Controversy exists regarding which should be done first, fracture fixation or arterial repair. The authors prefer placement of temporary intravascular shunts first with arterial occlusions to minimize ischemia during fracture treatment, with definitive vascular repair following. Rarely, immediate amputation may be considered due to the severity of orthopedic and neurovascular injuries. This is particularly true if primary nerve transection is present in addition to fracture and arterial injury.¹²⁶ Collaborative decision making by the trauma, orthopedic, and plastic/reconstructive team is essential.

Operative intervention for vascular injuries should follow standard principles of repair (see "Vascular Repair Techniques"). For subclavian or axillary artery repairs, 6-mm PTFE

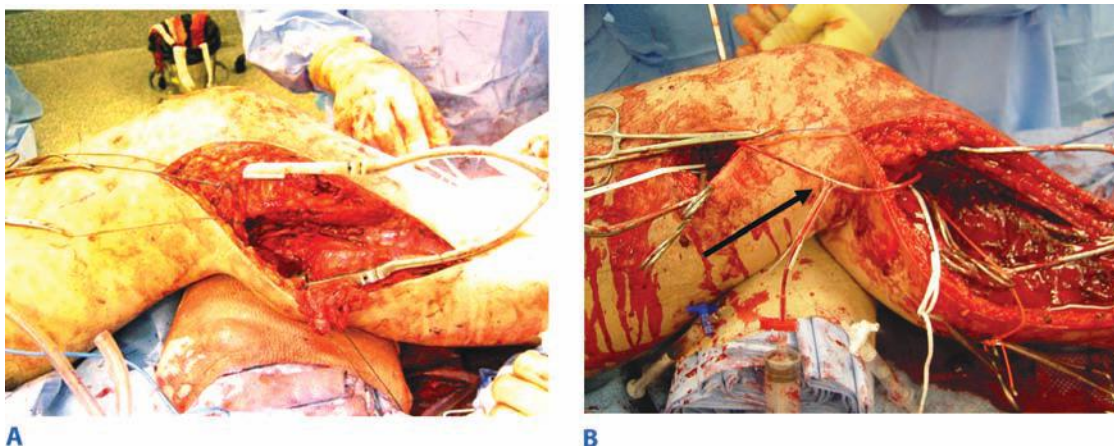


Figure 7-71. **A.** The popliteal space is commonly accessed using a single medial incision (the detached semitendinosus, semimembranosus, and gracilis muscles are identified by different suture types). **B.** Alternatively, a medial approach with two incisions may be used. Insertion of a Pruitt-Inahara shunt (*arrow*) provides temporary restoration of blood flow, which prevents ischemia during fracture treatment.

graft and RSVG are used. Because associated injuries of the brachial plexus are common, a thorough neurologic examination of the extremity is mandated before operative intervention. Operative approach for a brachial artery injury is via a medial upper extremity longitudinal incision; proximal control may be obtained at the axillary artery, and an S-shaped extension through the antecubital fossa provides access to the distal brachial artery. The injured vessel segment is excised, and an end-to-end interposition RSVG graft is performed. Upper extremity fasciotomy is rarely required unless the patient manifests preoperative neurologic changes or diminished pulse upon revascularization, or the time to operative intervention is extended. For SFA injuries, external fixation of the femur typically is performed, followed by end-to-end RSVG of the injured SFA segment. Close monitoring for calf compartment syndrome is mandatory. Preferred access to the popliteal space for an acute injury is the medial one-incision approach with detachment of the semitendinosus, semimembranosus, and gracilis muscles (Fig. 7-71). Another option is a medial approach with two incisions using a longer RSVG, but this requires interval ligation of the popliteal artery and geniculate branches. Rarely, with open wounds a straight posterior approach with an S-shaped incision can be used. If the patient has an associated popliteal vein injury, this should be repaired first with a PTFE interposition graft while the artery is shunted. For an isolated popliteal artery injury, RSVG is performed with an end-to-end anastomosis. Compartment syndrome is common, and presumptive four-compartment fasciotomies are warranted in patients with combined arterial and venous injury. Once the vessel is repaired and restoration of arterial flow documented, completion angiography should be done in the OR if there is no palpable distal pulse. Vasoparalysis with verapamil, nitroglycerin, and papaverine may be used to treat vasoconstriction (Table 7-11).

Compartment syndromes, which can occur anywhere in the extremities, involve an acute increase in pressure inside a closed space, which impairs blood flow to the structures within. Causes of compartment syndrome include arterial hemorrhage into a compartment, venous ligation or thrombosis, crush injuries, and reperfusion injury. In conscious patients, pain is the prominent symptom, and active or passive motion of muscles in the involved compartment increases the pain. Paresthesias may

Table 7-11

Arterial vasospasm treatment guideline

Step 1: Intra-arterial alteplase (tissue plasminogen activator) 5 mg/20 mL bolus If spasm continues, proceed to step 2.
Step 2: Intra-arterial nitroglycerin 200 µg/20 mL bolus Repeat same dose once as needed. If spasm continues, proceed to step 3.
Step 3: Inter-arterial verapamil 10 mg/10 mL bolus If spasm continues, proceed to step 4.
Step 4: Inter-arterial papaverine drip 60 mg/50 mL given over 15 min

also be described. In the lower extremity, numbness between the first and second toes is the hallmark of early compartment syndrome in the exquisitely sensitive anterior compartment and its enveloped deep peroneal nerve. Progression to paralysis can occur, and loss of pulses is a late sign. In comatose or obtunded patients, the diagnosis is more difficult to secure. In patients with a compatible history and a tense extremity, compartment pressures should be measured with a hand-held Stryker device. Fasciotomy is indicated in patients with a gradient of <35 mm Hg (gradient = diastolic pressure – compartment pressure), ischemic periods of >6 hours, or combined arterial and venous injuries. The lower extremity is most frequently involved, and compartment release is performed using a two-incision, four-compartment fasciotomy (Fig. 7-72). Of note, the soleus muscle must be detached from the tibia to decompress the deep flexor compartment.

SURGICAL INTENSIVE CARE MANAGEMENT

Postinjury Resuscitation

ICU management of the trauma patient, either with direct admission from the ED or after emergent operative intervention, is considered in distinct phases, because there are differing goals

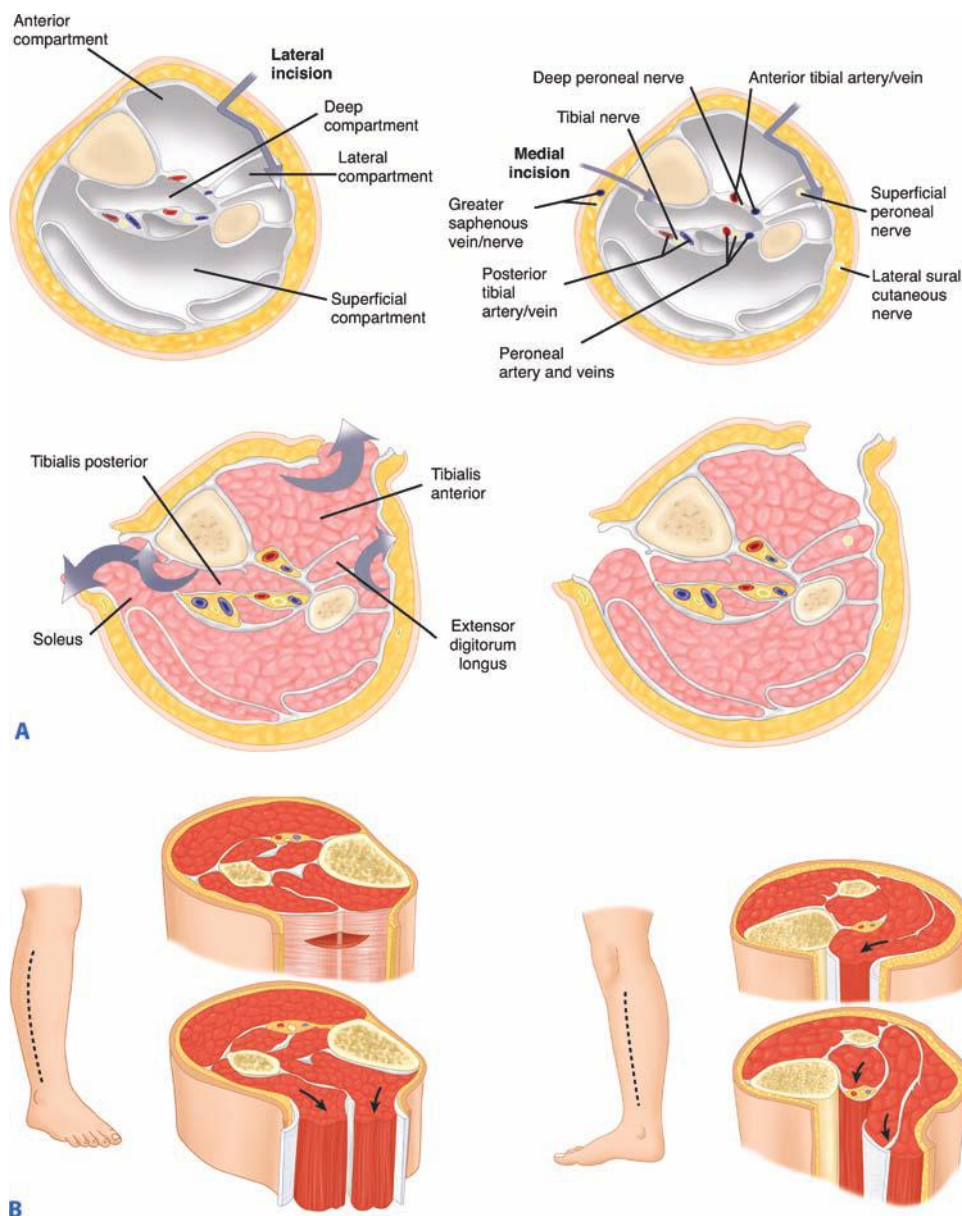


Figure 7-72. A. The anterior and lateral compartments are approached from a lateral incision, with identification of the fascial raphe between the two compartments. Care must be taken to avoid the superficial peroneal nerve running along the raphe. **B.** To decompress the deep flexor compartment, which contains the tibial nerve and two of the three arteries to the foot, the soleus muscle must be detached from the tibia.

and priorities. The period of acute resuscitation, typically lasting for the first 12 to 24 hours after injury, combines several key principles: optimizing tissue perfusion, ensuring normothermia, and restoring coagulation. There are a multitude of management algorithms aimed at accomplishing these goals, the majority of which involve goal-directed resuscitation with initial volume loading to attain adequate preload, followed by judicious use of inotropic agents or vasopressors.¹²⁷ Although the optimal hemoglobin level remains debated, during shock resuscitation a hemoglobin level of >10 g/dL is generally accepted to optimize hemostasis and ensure adequate oxygen delivery. After the first 24 hours of resuscitation, a more judicious transfusion trigger of a hemoglobin level of <7 g/dL in the euvoletic patient limits the adverse inflammatory effects of stored RBCs. The resuscitation of the severely injured trauma patient may require a considerable amount of crystalloid resuscitation, but recent trends have focused on limiting crystalloid loading. Although early colloid administration is appealing, evidence to date does not support this concept. In fact, optimizing crystalloid administra-

tion is a challenging aspect of early care (i.e., balancing cardiac performance against generation of an abdominal compartment syndrome and generalized tissue edema).

Invasive monitoring with pulmonary artery catheters is controversial but may be a necessary adjunct in occasional patients with multiple injuries who require advanced inotropic support. Not only do such devices allow minute-to-minute monitoring of the patient, but the added information on the patient's volume status, cardiac function, peripheral vascular tone, and metabolic response to injury permits appropriate therapeutic intervention. With added information on the patient's cardiac function, cardiac indices and oxygen delivery become important variables in the ongoing ICU management. Resuscitation to values of >500 mL/min per square meter for the oxygen delivery index and >3.8 L/min per square meter for the cardiac index are the goals.¹³³ Pulmonary artery catheters also enable the physician to monitor response to vasoactive agents. Although norepinephrine is the agent of choice for patients with low systemic vascular resistance who are unable to maintain a mean arterial

pressure of >60 mm Hg, patients may have an element of myocardial dysfunction requiring inotropic support. The role of relative adrenal insufficiency is another controversial area.

Optimal early resuscitation is mandatory and determines when the patient can undergo definitive diagnosis as well as when the patient can be returned to the OR after initial damage control surgery. Specific goals of resuscitation before repeated “semielective” transport include a core temperature of >35°C (95°F), base deficit of <6 mmol/L, and normal coagulation indices. Although correction of metabolic acidosis is desirable, how quickly this should be accomplished requires careful consideration. Adverse sequelae of excessive crystalloid resuscitation include increased intracranial pressure, worsening pulmonary edema, and intra-abdominal visceral and retroperitoneal edema resulting in secondary abdominal compartment syndrome. Therefore, it should be the overall trend of the resuscitation rather than a rapid reduction of the base deficit that is the goal. The goal is to normalize lactate within 24 hours.

In general, wounds sustained from trauma should be examined daily for progression of healing and signs of infection. Complex soft tissue wounds of the abdomen, such as degloving injuries after blunt trauma (termed *Morel-Lavallee lesions*), shotgun wounds, and other destructive blast injuries, are particularly difficult to manage. Following initial débridement of devitalized tissue, wound care includes wet-to-dry dressing changes twice daily or application of a VAC device. Repeated operative débridement may be necessary, and early involvement of the reconstructive surgery service for possible flap coverage is advised. Midline laparotomy wounds are inspected 48 hours postoperatively by removing the sterile surgical dressing. If an ileostomy or colostomy is required, one should inspect it daily to ensure that it is viable. If the patient develops high-grade fever, the wound should be inspected sooner to exclude an early necrotizing infection. If a wound infection is identified—as evidenced by erythema, pain along the wound, or purulent drainage—the wound should be widely opened by removing skin staples. After ensuring that the midline fascia is intact with digital palpation, the wound is initially managed with wet-to-dry dressing changes. The most common intra-abdominal complications are anastomotic failure and abscess. The choice between percutaneous and operative therapy is based on the location, timing, and extent of the collection.

Abdominal Compartment Syndrome

The abdominal compartment syndrome is classified as pathologic intra-abdominal hypertension due to intra-abdominal injury (primary) or splanchnic reperfusion after massive resuscitation (secondary). Secondary abdominal compartment syndrome may result from any condition requiring

10▶ extensive crystalloid resuscitation, including extremity trauma, chest trauma, or even postinjury sepsis. The sources of increased intra-abdominal pressure include gut edema, ascites, bleeding, and packs. A diagnosis of intra-abdominal hypertension cannot reliably be made by physical examination; therefore, it is obtained by measuring the intraperitoneal pressure. The most common technique is to measure the patient’s bladder pressure. Fifty milliliters of saline is instilled into the bladder via the aspiration port of the Foley catheter with the drainage tube clamped, and a three-way stopcock and water manometer is placed at the level of the pubic symphysis. Bladder pressure is then measured on the manometer in centimeters of water (Table 7-12) and correlated with the physiologic impact of abdominal compartment

Table 7-12

Abdominal compartment syndrome grading system

GRADE	BLADDER PRESSURE	
	mmHg	cm H ₂ O
I	10–15	13–20
II	16–25	21–35
III	26–35	36–47
IV	>35	>48

syndrome. Conditions in which the bladder pressure is unreliable include bladder rupture, external compression from pelvic packing, neurogenic bladder, and adhesive disease.

Increased abdominal pressure affects multiple organ systems (Fig. 7-73). Abdominal compartment syndrome, as noted earlier, is defined as intra-abdominal hypertension sufficient to produce physiologic deterioration and frequently manifests via such end-organ sequelae as decreased urine output, increased pulmonary inspiratory pressures, decreased cardiac preload, and increased cardiac afterload. Because any of these clinical symptoms of abdominal compartment syndrome may be attributed to the primary injury, a heightened awareness of this syndrome must be maintained. Organ failure can occur over a wide range of recorded bladder pressures. Generally, no specific bladder pressure prompts therapeutic intervention, except when the pressure is >35 mm Hg. Rather, emergent decompression is carried out when intra-abdominal hypertension reaches a level at which end-organ dysfunction occurs. Mortality is directly affected by the timing of decompression, with 60% mortality in patients undergoing presumptive decompression, 70% mortality in patients with a delay in decompression, and nearly uniform mortality in those not undergoing decompression. Usually decompression is performed operatively, either in the ICU if the patient is hemodynamically unstable or in the OR. ICU bedside laparotomy is easily accomplished, avoids transport of hemodynamically compromised patients, and requires minimal equipment (e.g., scalpel, suction device, cautery, and dressings for temporary abdominal closure). In patients with significant intra-abdominal fluid as the primary component of abdominal compartment syndrome, rather than bowel or retroperitoneal edema, decompression can be accomplished effectively via a percutaneous drain. This method is particularly applicable for nonoperative management of major liver injuries. These patients are identified by bedside ultrasound, and the morbidity of a laparotomy is avoided. When operative decompression is required with egress of the abdominal contents, temporary coverage is obtained using a subfascial 45 × 60 cm sterile drape and Ioban application (see Fig. 7-50).

The performance of damage control surgery and recognition of abdominal compartment syndrome have dramatically improved patient survival, but at the cost of an open abdomen. Several management points deserve attention. Despite having a widely open abdomen, patients can develop recurrent abdominal compartment syndrome, which increases their morbidity and mortality; therefore, bladder pressure should be monitored every 4 hours, with significant increases in pressures alerting the clinician to the possible need for repeat operative

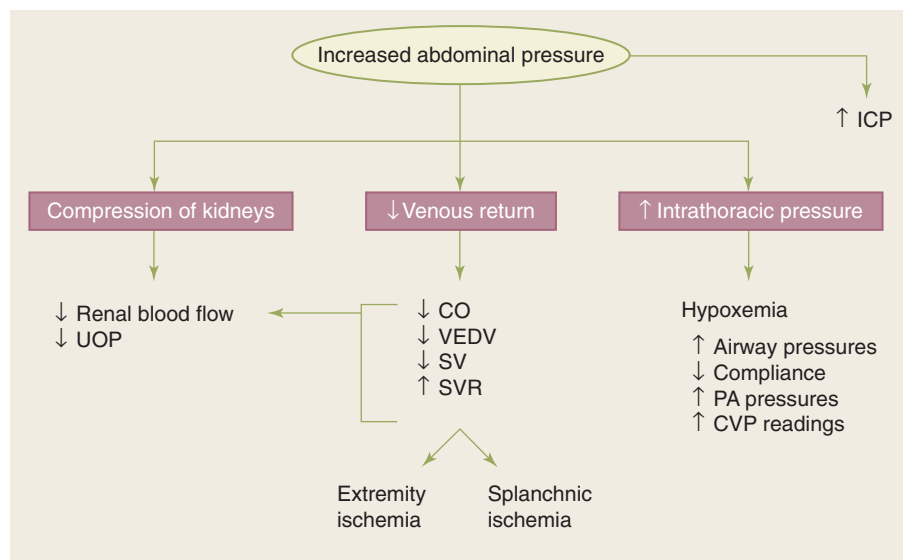


Figure 7-73. Abdominal compartment syndrome is defined by the end organ sequelae of intra-abdominal hypertension. CO = cardiac output; CVP = central venous pressure; ICP = intracranial pressure; PA = pulmonary artery; SV = stroke volume; SVR = systemic vascular resistance; UOP = urine output; VEDV = ventricular end-diastolic volume.

decompression. Patients with an open abdomen lose between 500 and 2500 mL per day of abdominal effluent. Appropriate volume compensation for this albumin-rich fluid remains controversial, with regard to both the amount administered (replacement based on clinical indices vs. routine ½ mL replacement for every milliliter lost) as well as the type of replacement (crystalloid vs. colloid).

Following resuscitation and management of specific injuries, the goal of the operative team is to close the abdomen as quickly as possible. Multiple techniques have been introduced to obtain fascial closure of the open abdomen to minimize morbidity and cost of care. Historically, for patients who could not be closed at repeat operation, approximation of the fascia with mesh (prosthetic or biologic) was used, with planned reoperation. Another option was split-thickness skin grafts applied directly to the exposed bowel for coverage; removal of the skin grafts was planned 9 to 12 months after the initial surgery, with definitive repair of the hernia by component separation. However, delayed abdominal wall reconstruction was resource intensive, with considerable patient morbidity. The advent of VAC technology has revolutionized fascial closure. The authors currently use a sequential closure technique with the wound VAC device that is based on constant fascial tension and return to the OR every 48 hours until closure is complete (Fig. 7-74).¹²⁸ The authors' success rate with this approach exceeds 95%. This is important because among patients not attaining fascial closure, 20% suffer GI tract complications that prolong their hospital course. These include intra-abdominal abscess, enteric fistula, and bowel perforations (Fig. 7-75). Management requires frequent operative or percutaneous drainage of abscesses, control of fistulas, and prolonged nutritional support.

SPECIAL POPULATIONS

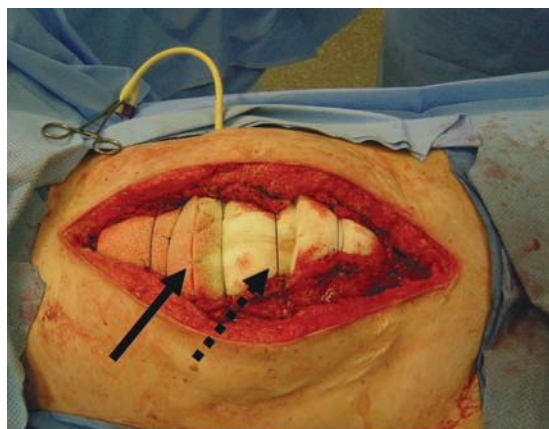
Pregnant Patients

During pregnancy, 7% of women are injured. Motor vehicle collisions and falls are the leading causes of injury, accounting for 70% of cases. Fetal death after trauma most frequently occurs after motor vehicle collisions, but only 11% of fetal deaths are

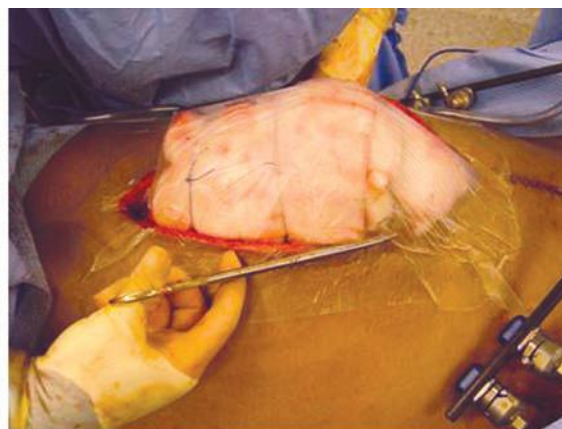
due to the death of the mother; therefore, early trauma resuscitation and management is directed not only at the mother but also at the fetus. Domestic violence is also common, affecting between 10% and 30% of pregnant women and resulting in fetal mortality of 5%.

Pregnancy results in physiologic changes that may impact postinjury evaluation (Table 7-13). Heart rate increases by 10 to 15 beats per minute during the first trimester and remains elevated until delivery. Blood pressure diminishes during the first two trimesters due to a decrease in systemic vascular resistance and rises again slightly during the third trimester (mean values: first = 105/60, second = 102/55, third = 108/67). Intravascular volume is increased by up to 8 L, which results in a relative anemia but also a relative hypervolemia. Consequently a pregnant woman may lose 35% of her blood volume before exhibiting signs of shock. Pregnant patients have an increase in tidal volume and minute ventilation but a decreased functional residual capacity; this results in a diminished PCO_2 and respiratory alkalosis. Also, pregnant patients may desaturate more rapidly, particularly in the supine position and during intubation. Supplemental oxygen is always warranted in the trauma patient but is particularly critical in the injured pregnant patient, because the oxygen dissociation curve is shifted to the left for the fetus compared to the mother (i.e., small changes in maternal oxygenation result in larger changes for the fetus because the fetus is operating in the steep portions of the dissociation curve). Anatomic changes contribute to these pulmonary functional alterations and are relevant in terms of procedures. With the gravid uterus enlarged, DPL should be performed in a supra-umbilical site with the catheter directed cephalad. In addition, the upward pressure on the diaphragm calls for caution when placing a thoracostomy tube; standard positioning may result in an intra-abdominal location or perforation of the diaphragm.

Other physiologic changes during pregnancy affect the GI, renal, and hematologic systems. The lower esophageal sphincter has decreased competency, which increases the risk for aspiration. Liver function test values increase, with the alkaline phosphatase level nearly doubling. The high levels of progesterone impair gallbladder contractions, which results in bile stasis and an increased incidence of gallstone formation; this may not



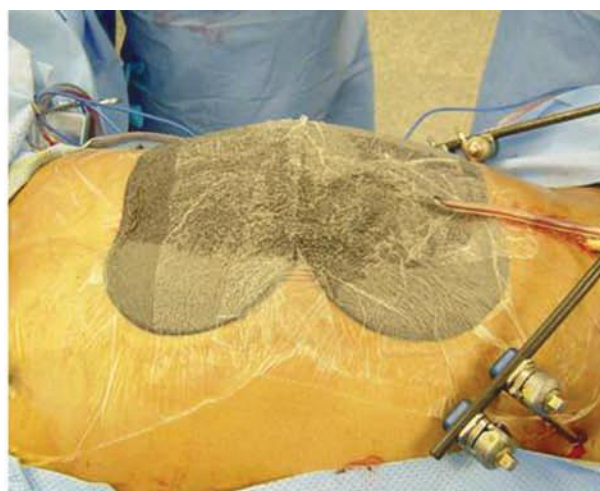
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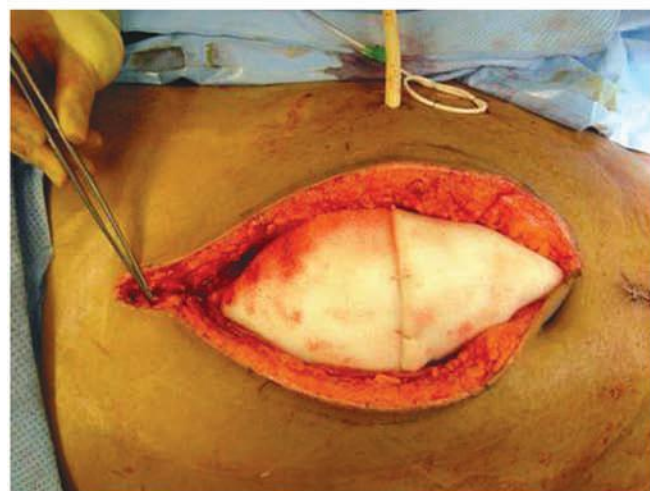
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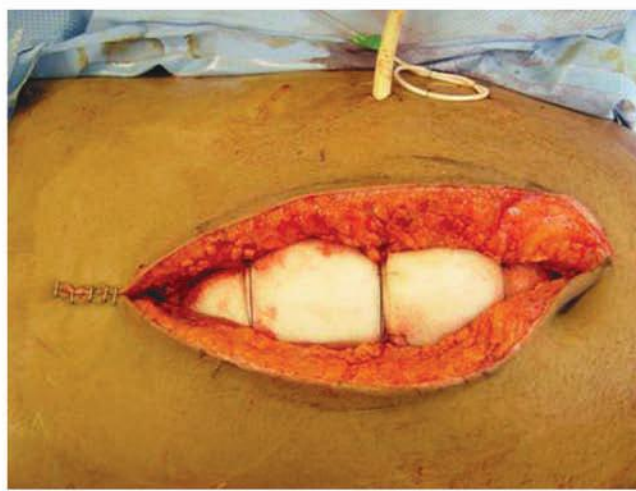
C



D



E



F

Figure 7-74. The authors' sequential closure technique for the open abdomen. **A.** Multiple white sponges (*solid arrow*), stapled together, are placed on top of the bowel underneath the fascia. Interrupted No. 1 polydioxanone sutures are placed approximately 5 cm apart (*dashed arrow*), which puts the fascia under moderate tension over the white sponge. **B.** After the sticky clear plastic vacuum-assisted closure (VAC) dressing is placed over the white sponges and adjacent 5 cm of skin, the central portion is removed by cutting along the wound edges. **C** and **D.** Black VAC sponges are placed on top of the white sponges and plastic-protected skin with standard occlusive dressing and suction. **E.** On return to the operating room (OR) 48 hours later, fascial sutures are placed from both the superior and inferior directions until tension precludes further closure; skin is closed over the fascial closure with skin staples. **F.** White sponges (fewer in number) are again applied and fascial retention sutures are placed with planned return to the OR in 48 hours.



A



B

Figure 7-75. Complications after split-thickness skin graft closure of the abdomen include enterocutaneous fistulas (intubated here with a red rubber catheter) (A; arrow) and rupture of the graft with exposure of the bowel mucosa (B).

affect the trauma bay evaluation but becomes important in a prolonged ICU stay. Plasma albumin level decreases from a normal of around 4.3 g/dL to an average of 3.0 g/dL. Renal blood flow increases by 30% during pregnancy, which causes a decrease in serum level of blood urea nitrogen and creatinine. The uterus may also compress the ureters and bladder, causing hydronephrosis and hydroureter. Finally, as noted earlier there is a relative anemia during pregnancy, but a hemoglobin level of <11 g/dL

Table 7-13

Physiologic effects of pregnancy

Cardiovascular

- Increase in heart rate by 10–15 bpm
- Decreased systemic vascular resistance resulting in:
 - (a) Increased intravascular volume
 - (b) Decreased blood pressure during the first two trimesters

Pulmonary

- Elevated diaphragm
- Increased tidal volume
- Increased minute ventilation
- Decreased functional residual capacity

Hematopoietic

- Relative anemia
- Leukocytosis
- Hypercoagulability
 - (a) Increased levels of factors VII, VIII, IX, X, XII
 - (b) Decreased fibrinolytic activity

Other

- Decreased competency of lower esophageal sphincter
- Increased enzyme levels on liver function tests
- Impaired gallbladder contractions
- Decreased plasma albumin level
- Decreased blood urea nitrogen and creatinine levels
- Hydronephrosis and hydroureter

is considered abnormal. Additional hematologic changes include a moderate leukocytosis (up to 20,000 mm³) and a relative hypercoagulable state due to increased levels of factors VII, VIII, IX, X, and XII and decreased fibrinolytic activity.

During evaluation in the ED, the primary and secondary surveys commence, with mindfulness that the mother always receives priority while conditions are still optimized for the fetus.¹²⁹ This management includes provision of supplemental oxygen (to prevent maternal and fetal hypoxia), aggressive fluid resuscitation (the hypervolemia of pregnancy may mask signs of shock), and placement of the patient in the left lateral decubitus position (or tilting of the backboard to the left) to avoid caval compression. Assessment of the fetal heart rate is the most valuable information regarding fetal viability. Fetal monitoring should be performed with a cardiotocographic device that measures both contractions and fetal heart tones (FHTs). Because change in heart rate is the primary response of the fetus to hypoxia or hypotension, anything above an FHT of 160 is a concern, whereas bradycardia (FHT of <120) is considered fetal distress. Ideally, if possible, a member of the obstetrics team should be present during initial evaluation to perform a pelvic examination using a sterile speculum. Vaginal bleeding can signal early cervical dilation and labor, abruptio placentae, or placenta previa. Amniotic sac rupture can result in prolapse of the umbilical cord with fetal compromise. Strong contractions are associated with true labor and should prompt consideration of delivery and resuscitation of the neonate. Focused prenatal history taking should elicit a history of pregnancy-induced hypertension, gestational diabetes, congenital

heart disease, preterm labor, or placental abnormalities. Asking the patient when the baby first moved and if she is currently experiencing movement of the fetus is important. Determining fetal age is key for considerations of viability. Gestational age may be estimated by noting fundal height, with the fundus approximating the umbilicus at 20 weeks and the costal margin at 40 weeks. Discrepancy in dates and size may be due to uterine rupture or hemorrhage.

Initial evaluation for abdominopelvic trauma in pregnant patients should proceed in the standard manner. Ultrasound (FAST) of the abdomen should evaluate the four windows (pericardial, right and left upper quadrant, and bladder) and additionally assess FHTs, fetal movement, and sufficiency of amniotic fluid. DPL can be performed in pregnant women via a supraumbilical, open technique. Trauma radiography of pregnant patients presents a conundrum. Radiation damage has three distinct phases of damage and effect: preimplantation, during the period of organogenesis from 3 to 16 weeks, and after 16 weeks. Generally, it is accepted that “safe” doses of radiation from radiography are <5 rad.¹³⁰ A chest radiograph results in a dose of 0.07 mrad; CT scan of the chest, <1 rad; and CT scan of the abdomen, 3.5 rad. It is important, therefore, to limit radiographs to those that are essential and to shield the pelvis with a lead apron when possible. If clinically warranted, however, a radiograph should be obtained.

The vast majority of injuries are treated similarly whether the patient is pregnant or not. Following standard protocols for nonoperative management of blunt trauma avoids the risks associated with general anesthesia. A particular challenge in the pregnant trauma patient is a major pelvic fracture. Because uterine and retroperitoneal veins may dilate to 60 times their original size, hemorrhage from these vessels may be torrential. Fetal loss may be related to both maternal shock and direct injury to the uterus or fetal head. Penetrating injuries in this patient population also carry a high risk. The gravid uterus is a large target, and any penetrating injury to the abdomen may result in fetal injury depending on trajectory and uterine size. Gunshot wounds to the abdomen are associated with a 70% injury rate to the uterus and 35% mortality rate of the fetus. If the bullet traverses the uterus and the fetus is viable, cesarean section should be performed. On the other hand, stab wounds do not often penetrate the thick wall of the uterus. Indications for emergent cesarean section include: (a) severe maternal shock or impending death (if the fetus is delivered within 5 minutes, survival is estimated at 70%), (b) uterine injury or significant fetal distress (anticipated survival rates of >70% if FHTs are present and fetal gestational age is >28 weeks).¹³¹

Any patient with a viable pregnancy should be monitored after trauma, with the length of monitoring determined by the injury mechanism and patient physiology. Patients who are symptomatic, defined by the presence of uterine irritability or contractions, abdominal tenderness, vaginal bleeding, or blood pressure instability, should be monitored in the hospital for at least 24 hours. In addition, patients at high risk for fetal loss (those experiencing vehicle ejection or involved in motorcycle or pedestrian collisions and those with maternal tachycardia, Injury Severity Score of >9, gestational period of >35 weeks, or history of prior assault) also warrant careful monitoring.¹³² Patients without these risk factors who are asymptomatic can be monitored for 6 hours in the ED and sent home if no problems develop. They should be counseled regarding warning signs that mandate prompt return to the ED.

Geriatric Patients

Elderly trauma patients (>65 years of age) are hospitalized twice as often as those in any other age group, and this population accounts for one quarter of all trauma admissions. Although the physiology of aging separates older trauma patients from the younger generation (Table 7-14), treatment must remain individualized (some octogenarians look and physiologically act 50 years old, whereas others appear closer to 100 years). No chronologic age is associated with a higher morbidity or mortality, but a patient’s comorbidities do impact the individual’s postinjury course and outcome. For example, recognition that a patient is taking beta blockers affects the physician’s evaluation of vital signs in the ED and impacts treatment course in the ICU. Early monitoring of arterial blood gas values will identify occult shock. A base deficit of >6 mmol/L is associated with a twofold higher risk of mortality in patients over the age of 55 than in younger patients (67% vs. 30%).¹³³

Although the published literature on geriatric traumatic brain injury is relatively sparse and uncontrolled with regard to management, some interesting points are noted. First, outcomes are worse in this age group than in their younger counterparts. Based on data from the Traumatic Coma Databank, mortality in patients with severe head injury more than doubles after the age of 55. Moreover, 25% of patients with a normal GCS score of 15 had intracranial bleeding, with an associated mortality of 50%.¹²³ Just as there is no absolute age that predicts outcome, admission GCS score is a poor predictor of individual outcome.

Table 7-14

Physiologic effects of aging

Cardiovascular

Increased prevalence of heart disease

Fatty deposition in the myocardium, resulting in:

- (a) Progressive stiffening and loss of elasticity
- (b) Diminished stroke volume, systolic contraction, and diastolic relaxation

Decrease in cardiac output of 0.5% per year

Atherosclerotic disease that limits cardiac response to stress

Increased risk of coronary ischemia

Thickening and calcification of the cardiac valves, which results in valvular incompetence

Pulmonary

Loss of compliance

Progressive loss of alveolar size and surface area

Air trapping and atelectasis

Intracranial

Loss of cerebral volume, resulting in:

- (a) Increased risk of tearing of bridging veins with smaller injuries
- (b) Accumulation of a significant amount of blood before symptoms occur

Senescence of the senses

Other

Decline in creatinine clearance by 80%–90%

Osteoporosis, which causes a greater susceptibility to fractures

Therefore, the majority of trauma centers advocate an initial aggressive approach with re-evaluation at the 72-hour mark to determine subsequent care.

One of the most common sequelae of blunt thoracic trauma is rib fractures. In the aging population, perhaps due to osteoporosis, less force is required to cause a fracture. In fact, in one study, 50% of patients >65 years old sustained rib fractures from a fall of <6 ft, compared with only 1% of patients <65 years of age. Concurrent pulmonary contusion is noted in up to 35% of patients, and pneumonia complicates the injuries in 10% to 30% of patients with rib fractures, not surprisingly leading to longer ICU stays.^{135,136} Additionally, mortality increases linearly with the number of rib fractures. Patients who sustain more than six rib fractures have pulmonary morbidity rates of >50% and overall mortality rates of >20%.

Chronologic age is not the best predictor of outcome, but the presence of pre-existing conditions, which affect a patient's physiologic age, is associated with increased mortality rates. Injury Severity Score is probably the best overall predictor of patient outcome in the elderly; however, for any given individual its sensitivity may not be precise, and there is a time delay in obtaining sufficient information to calculate the final score. In addition to pre-existing conditions and severity of injury, the occurrence of complications compounds the risk for mortality.

Pediatric Patients

Twenty million children, or almost one in four children, are injured each year, with an associated cost of treating the injured child of \$16 billion per year. Injury is the leading cause of death among children over the age of 1 year, with 15,000 to 25,000 pediatric deaths per year. Disability after traumatic injury is more devastating, with rates 3 to 10 times that of the death rate. Pediatric trauma involves different mechanisms, different constellations of injury, and the potential for long-term problems related to growth and development. As with adult trauma, over 85% of pediatric trauma has a blunt mechanism, with boys injured twice as often as girls.¹³⁷ Falls are the most common cause of injury in infants and toddlers. In children, bicycle mishaps are the most common cause of severe injury, whereas motor vehicle-related injury predominates in adolescence. Although unintentional injuries are by far the most common type of injuries in childhood, the number of intentional injuries, such as firearm-related injury and child abuse, is increasing.

ED preparation for the pediatric trauma patient includes assembling age-appropriate equipment (e.g., intubation equipment; IV catheters, including intraosseous needles and 4F single-lumen lines), laying out the Broselow Pediatric Emergency Tape (which allows effective approximation of the patient's weight, medication doses, size of endotracheal tube, and chest tube size), and turning on heat lamps. Upon the pediatric patient's arrival, the basic tenets of the ABCs apply, with some caveats. In children, the airway is smaller and more cephalad in position compared with that of adults, and in children younger than 10 years, the larynx is funnel shaped rather than cylindrical as in adults. Additionally, the child's tongue is much larger in relation to the oropharynx. Therefore, a small amount of edema or obstruction can significantly reduce the diameter of the airway (thus increasing the work of breathing), and the tongue may posteriorly obstruct the airway, causing intubation to be difficult. During intubation, a Miller (straight) blade rather than a Macintosh (curved) blade may be more effective due to the acute angle of the cephalad, funnel-shaped larynx. Administration

of atropine before rapid-sequence intubation will prevent bradycardia. Adequate ventilation is critical, because oxygen consumption in infants and young children is twice that in adults; onset of hypoxemia, followed by cardiac arrest, may be precipitous. Because gastric distension can inhibit adequate ventilation, placement of a nasogastric tube may facilitate effective gas exchange. Approximately one third of preventable deaths in children are related to airway management; therefore, if airway control cannot be obtained using a standard endotracheal method, surgical establishment of an airway should be considered. In children older than 11 years, standard cricothyroidotomy is performed. Due to the increased incidence of subglottic stenosis in younger patients, needle cricothyroidotomy with either a 14- or 16-gauge catheter is advocated, although it is rarely used. Alternatively, tracheostomy may be performed. In children, the standard physiologic response to hypovolemia is peripheral vasoconstriction and reflex tachycardia; this may mask significant hemorrhagic injury, because children can compensate for up to a 25% loss of circulating blood volume with minimal external signs. "Normal" values for vital signs should not necessarily make one feel more secure about the child's volume status. Volume restoration is based on the child's weight; two to three boluses of 20 mL/kg of crystalloid is appropriate.

After initial evaluation based on the trauma ABCs, identification and management of specific injuries proceeds. Acute traumatic brain injury is the most common cause of death and disability in any pediatric age group. Although falls are the most common mechanism overall, severe brain injury most often is due to child abuse (in children <2 years) or motor vehicle collisions (in those >2 years). Head CT should be performed to determine intracranial pathology, followed by skull radiography to diagnose skull fractures. As in adults, CPP is monitored, and appropriate resuscitation is critical to prevent the secondary insults of hypoxemia and hypovolemia. Although some data indicate that the pediatric brain recovers from traumatic injury better than the adult brain, this advantage may be eliminated if hypotension is allowed to occur.

As is true in adults, the vast majority of thoracic trauma is also blunt. However, because a child's skeleton is not completely calcified, it is more pliable. Significant internal organ damage may occur without overlying bony fractures. For example, adult patients with significant chest trauma have a 70% incidence of rib fractures, whereas only 40% of children with significant chest trauma do. Pneumothorax is treated similarly in the pediatric population; patients who are asymptomatic with a pneumothorax of <15% are admitted for observation, whereas those who have a pneumothorax of >15% or who require positive pressure ventilation undergo tube decompression. Presence of a hemothorax in this age group may be particularly problematic, because the child's chest may contain his or her entire blood volume. If the chest tube output is initially 20% of the patient's blood volume (80 mL/kg) or is persistently >1 to 2 mL/kg per hour, thoracotomy should be considered. Aortic injuries are rare in children, and tracheobronchial injuries are more amenable to nonoperative management. Thoracic injuries are second only to brain injuries as the main cause of death according to the National Pediatric Trauma Registry; however, the overall mortality rate of 15% correlates with the levels in many adult studies.

The evaluation for abdominal trauma in the pediatric patient is similar to that in the adult. FAST is valid in the pediatric

age group to detect intra-abdominal fluid.¹³⁸ The mechanism of injury often correlates with specific injury patterns. A child sustaining a blow to the epigastrium (e.g., hitting the handlebars during a bike accident) should be evaluated for a duodenal hematoma and/or a pancreatic transection. After a motor vehicle collision in which the patient was wearing a passenger restraint, injuries comprising the “lap belt complex” or “seat belt syndrome” (i.e., abdominal wall contusion, small bowel perforation, flexion-distraction injury of the lumbar spine, diaphragm rupture, and occasionally abdominal aortic dissection) may exist. Nonoperative management of solid organ injuries, first used in children, is the current standard of care in the hemodynamically stable patient. If the patient shows clinical deterioration or hemodynamic lability, has a hollow viscus injury, or requires >40 mL/kg of packed RBCs, continued nonoperative management is not an option. Success rates of nonoperative management approach 95%, with an associated 10% to 23% transfusion rate. Blood transfusion rates, however, are significantly lower in patients managed nonoperatively than in patients undergoing operation (13% vs. 44%).¹³⁹

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chapter

Burns

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Surgical care of the burned patient has evolved into a specialized field incorporating the interdisciplinary skills of burn surgeons, nurses, therapists, and other healthcare specialists. However, recent mass casualty events have been a reminder that healthcare systems may be rapidly pressed to care for large numbers of burn patients. Naturally, general surgeons may be at the forefront in these events, so it is crucial that they are comfortable with the care of burned patients and well equipped to provide standard of care.

BACKGROUND

Burn injury historically carried a poor prognosis. With advances in fluid resuscitation¹ and the advent of early excision of the burn wound,² survival has become an expectation even for patients with severe burns. Continued improvements in critical care and progress in skin bioengineering herald a future in which functional and psychological outcomes are equally important as survival alone. With this shift in priority, the American Burn Association (ABA) has emphasized referral to specialized burn centers after early stabilization. Specific criteria should guide transfer of patients with more complex injuries or other medical needs to a burn center (Table 8-1). The ABA has published standards of care³ and created a verification process to ensure that burn centers meet those standards.⁴ Because of increased prehospital safety measures, burn patients are being transferred longer distances to receive definitive care at regional burn centers⁵; recent data from one burn center with a particularly wide catchment area confirmed that even transport times averaging 7 hours did not affect the long-term outcomes of burn patients.⁶

INITIAL EVALUATION

Initial evaluation of the burned patient involves four crucial assessments: airway management, evaluation of other injuries, estimation of burn size, and diagnosis of CO and cyanide poisoning. With direct thermal injury to the upper airway or smoke inhalation, rapid and severe airway edema is a potentially lethal threat. Anticipating the need for intubation and establishing an

early airway are critical. Perioral burns and singed nasal hairs are signs that the oral cavity and pharynx should be further evaluated for mucosal injury, but these physical findings alone do not indicate an upper airway injury. Signs of impending respiratory compromise may include a hoarse voice, wheezing, or stridor; subjective dyspnea is a particularly concerning symptom and should trigger prompt elective endotracheal intubation. In patients with combined multiple trauma, especially oral trauma, nasotracheal intubation may be useful but should be avoided if oral intubation is safe and easy.

Burned patients should be first considered trauma patients, especially when details of the injury are unclear. A primary survey should be conducted in accordance with Advanced Trauma Life Support guidelines. Concurrently with the primary survey, large-bore peripheral intravenous (IV) catheters should be placed and fluid resuscitation should be initiated; for a burn larger than 40% total body surface area (TBSA), two large-bore IVs are ideal. IV placement through burned skin is safe and effective but requires attention to securing the catheters. Central venous access may provide useful information as to volume status and be useful in severely burned patients. Rarely, IV resuscitation is indicated in patients with burns smaller than 15% who can usually hydrate orally. Pediatric patients with burns larger than 15% may require intraosseous access in emergent situations if venous access cannot be attained. An early and comprehensive secondary survey must be performed on all burn patients, but especially those with a history of associated trauma such as with a motor vehicle collision. Also, patients from structural fires in which the manner of egress is not known should be carefully evaluated for injuries from a possible jump or fall. Urgent radiology studies, such as a chest x-ray, should be performed in the emergency department, but nonurgent skeletal evaluation (i.e., extremity x-rays) can be done in the intensive care unit (ICU) to avoid hypothermia and delays in burn resuscitation. Hypothermia is a common prehospital complication that contributes to resuscitation failure. Patients should be wrapped with clean blankets in transport. Cooling blankets should be avoided in patients with moderate or large (>20% TBSA) burns.

Key Points

- 1▶ Follow American Burn Association criteria for transfer of a patient to a regional burn center.
- 2▶ Never administer prophylactic antibiotics other than tetanus vaccination.
- 3▶ Early excision and grafting of full-thickness and deep partial-thickness burns improve outcomes.

- 4▶ Intravenous fluid resuscitation for patients with burns greater than 20% of total body surface area (children with burns >15% of total body surface area) should be titrated to mean arterial pressure (MAP) greater than 60 mmHg and urine output greater than 30 mL/h.

Patients with acute burn injuries should never receive prophylactic antibiotics. This intervention has been clearly demonstrated to promote development of fungal infections and resistant organism and was abandoned in the mid-1980s. A tetanus booster should be administered in the emergency room.

The importance of pain management for these patients has been widely recognized over the past 25 years. However, we must also consider treatment of long-term anxiety. Therefore, it is important to administer an anxiolytic such as a benzodiazepine with the initial narcotics.

Most burn resuscitation formulas estimate fluid requirements using the burn size as a percentage of TBSA (%TBSA). The “rule of nines” is a crude but quick and effective method of estimating burn size (Fig. 8-1). In adults, the anterior and posterior trunk each account for 18%, each lower extremity is 18%, each upper extremity is 9%, and the head is 9%. In children under 3 years old, the head accounts for a larger relative surface area and should be taken into account when estimating burn size. Diagrams such as the Lund and Browder chart give a more accurate accounting of the true burn size in children. The importance of an accurate burn size assessment cannot be overemphasized. Superficial or first-degree burns should not be included when calculating the %TBSA, and thorough cleaning of soot and debris is mandatory to avoid confusing

soiled skin with burns. Examination of referral data suggests that physicians inexperienced with burns tend to overestimate the size of small burns and underestimate the size of large burns, with potentially detrimental effects on pretransfer resuscitation.⁷

An important contributor to early mortality in burn patients is carbon monoxide (CO) poisoning resulting from smoke inhalation. The affinity of CO for hemoglobin is approximately 200 to 250 times more than that of oxygen, which decreases the levels of normal oxygenated hemoglobin and can quickly lead to anoxia and death.⁸ Unexpected neurologic symptoms should raise the level of suspicion, and an arterial carboxyhemoglobin level must be obtained because pulse oximetry can be falsely elevated. Administration of 100% oxygen is the gold standard for treatment of CO poisoning and reduces the half-life of CO from 250 minutes in room air to 40 to 60 minutes on 100% oxygen.⁹ Some authors have proposed hyperbaric oxygen as an adjunctive therapy for CO poisoning.¹⁰ However, the data are mixed regarding the success of hyperbaric oxygen, and its associated logistical difficulties and complications have limited its usefulness for patients with moderate or large burns.^{11,12} Patients who sustain a cardiac arrest as a result of their CO poisoning have an extremely poor prognosis regardless of the success of initial resuscitation attempts.¹³ Hydrogen cyanide toxicity may also be a component of smoke inhalation injury. Afflicted patients may have a persistent lactic acidosis or ST elevation on electrocardiogram (ECG).¹⁴ Cyanide inhibits cytochrome oxidase, which is required for oxidative phosphorylation.¹⁵ Treatment consists of sodium thiosulfate, hydroxocobalamin, and 100% oxygen. Sodium thiosulfate works by transforming cyanide into a nontoxic thiocyanate derivative, but it works slowly and is not effective for acute therapy. Hydroxocobalamin quickly complexes with cyanide, is excreted by the kidney, and is recommended for immediate therapy.⁹ In the majority of patients, the lactic acidosis will resolve with ventilation, and sodium thiosulfate treatment becomes unnecessary.¹⁶

Table 8-1

Guidelines for referral to a burn center

Partial-thickness burns greater than 10% TBSA
Burns involving the face, hands, feet, genitalia, perineum, or major joints
Third-degree burns in any age group
Electrical burns, including lightning injury
Chemical burns
Inhalation injury
Burn injury in patients with complicated pre-existing medical disorders
Patients with burns and concomitant trauma in which the burn is the greatest risk. If the trauma is the greater immediate risk, the patient may be stabilized in a trauma center before transfer to a burn center.
Burned children in hospitals without qualified personnel for the care of children
Burn injury in patients who will require special social, emotional, or rehabilitative intervention
TBSA = total body surface area.

CLASSIFICATION OF BURNS

Burns are commonly classified as thermal, electrical, or chemical burns, with thermal burns consisting of flame, contact, or scald burns. Flame burns are not only the most common cause for hospital admission of burns, but also have the highest mortality. This is primarily related to their association with structural fires and the accompanying inhalation injury and/or CO poisoning.¹⁷

Electrical burns make up only 4% of U.S. hospital admissions but have special concerns including the potential for cardiac arrhythmias and compartment syndromes with concurrent rhabdomyolysis. A baseline ECG is recommended in all patients

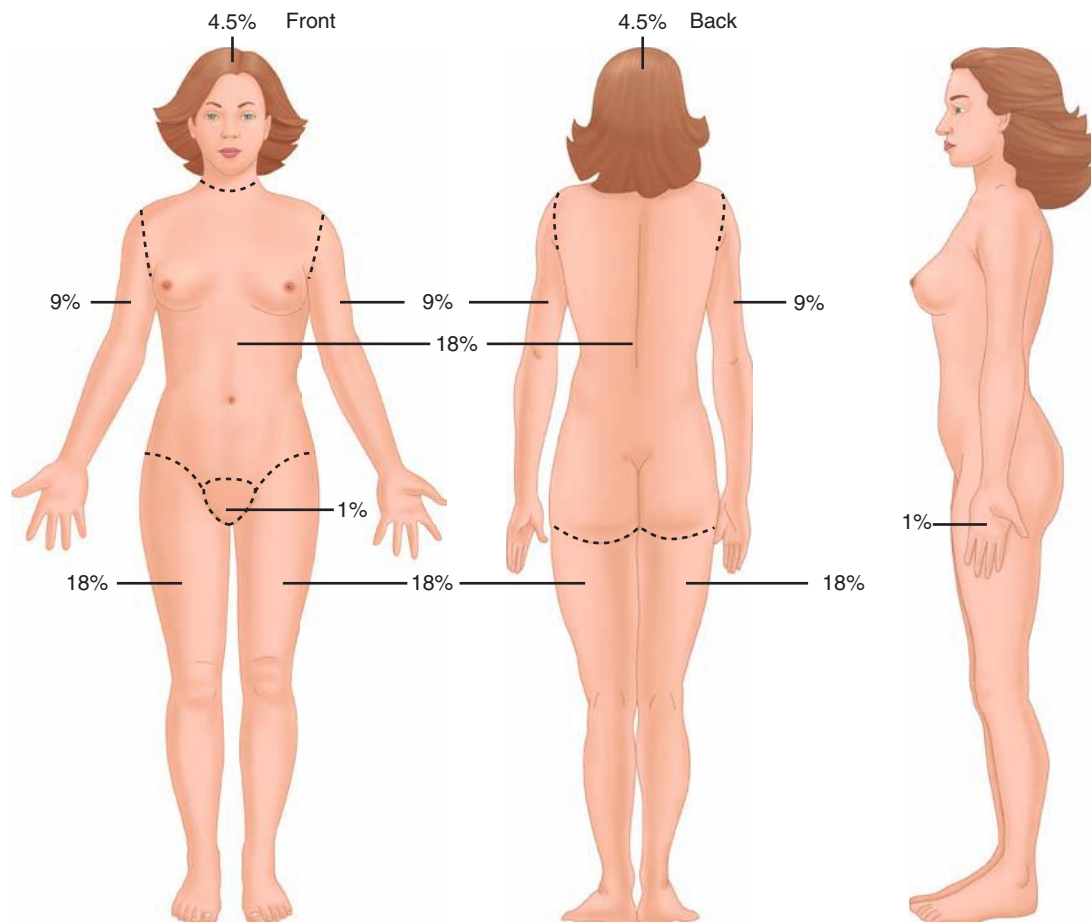


Figure 8-1. The “rule of nines” can be used as a quick reference for estimating a patient’s burn size by dividing the body into regions to which total body surface area is allocated in multiples of nine.

with an electrical injury, and a normal ECG in a low-voltage injury may preclude hospital admission. Because compartment syndrome and rhabdomyolysis are common in high-voltage electrical injuries, vigilance must be maintained for neurologic or vascular compromise, and fasciotomies should be performed even in cases of moderate clinical suspicion. Long-term neurologic and visual symptoms are not uncommon with high-voltage electrical injuries, and ophthalmologic and neurologic consultation should be obtained to better define a patient’s baseline function.¹⁸

Chemical burns are less common but potentially severe burns. The most important components of initial therapy are careful removal of the toxic substance from the patient and irrigation of the affected area with water for a minimum of 30 minutes, except in cases of concrete powder or powdered forms of lye, which should be swept from the patient to avoid activating the aluminum hydroxide with water. The offending agents in chemical burns can be systemically absorbed and may cause specific metabolic derangements. Formic acid has been known to cause hemolysis and hemoglobinuria, and hydrofluoric acid causes hypocalcemia. Hydrofluoric acid is a particularly common offender due to its widespread industrial uses. Calcium-based therapies are the mainstay of treating hydrofluoric acid burns, with topical application of calcium gluconate onto wounds¹⁹ and IV administration of calcium gluconate for systemic symptoms. Intra-arterial calcium gluconate infusion provides effective treatment of progressive tissue injury and intense pain.^{20,21} Patients undergoing intra-arterial therapy need

continuous cardiac monitoring. Persistent refractory hypocalcemia with electrocardiac abnormalities may signal the need for emergent excision of the burned areas.

BURN DEPTH

Based on the original burn depth classification by Dupuytren in 1832,²² burn wounds are commonly classified as superficial (first-degree), partial-thickness (second-degree), full-thickness (third-degree), and fourth-degree burns, which affect underlying soft tissue. Partial-thickness burns are classified as either superficial or deep partial-thickness burns by depth of involved dermis. Clinically, first-degree burns are painful but do not blister, second-degree burns have dermal involvement and are extremely painful with weeping and blisters, and third-degree burns are leathery, painless, and nonblanching. Jackson described three zones of tissue injury following burn injury.²³ The zone of coagulation is the most severely burned portion and is typically in the center of the wound. As the name implies, the affected tissue is coagulated and sometimes frankly necrotic, much like a third- or fourth-degree burn, and will need excision and grafting. Peripheral to that is a zone of stasis, with variable degrees of vasoconstriction and resultant ischemia, much like a second-degree burn. Appropriate resuscitation and wound care may help prevent conversion to a deeper wound, but infection or suboptimal perfusion may result in an increase in burn depth. This is clinically relevant because many superficial partial-thickness burns will heal with expectant management, and the

3▶ majority of deep partial-thickness burns require excision and skin grafting. The last area of a burn is called the zone of hyperemia, which will heal with minimal or no scarring and is most like a superficial or first-degree burn.

Unfortunately, even experienced burn surgeons have limited ability to accurately predict the healing potential of partial-thickness burns soon after injury; one reason is that burn wounds evolve over the 48 to 72 hours after injury. Numerous techniques have been developed with the idea that better early prediction of burn depth will expedite appropriate surgical decision making. One of the most effective ways to determine burn depth is full-thickness biopsy, but this has several limitations; not only is the procedure painful and potentially scarring, but accurate interpretation of the histopathology requires a specialized pathologist and may have slow turnaround times.²⁴ Laser Doppler can measure skin perfusion to predict burn depth with a positive predictive value of up to 80% in some studies.^{25,26} Noncontact ultrasound has been postulated as a painless modality to predict nonhealing wounds and has the advantage of easily performed serial measurements.²⁷ Unfortunately, none of these newer therapies have proven adequately superior to justify their cost and as yet have not substituted serial examination by experienced burn surgeons.

PROGNOSIS

The Baux score (mortality risk equals age plus %TBSA) was used for many years to predict mortality in burns. Analysis of multiple risk factors for burn mortality has validated age and %TBSA as the strongest predictors of mortality.²⁸ Advancements in burn care have lowered overall mortality to the point that the Baux score may no longer be accurate. However, age and burn size, as well as inhalation injury, continue to be the most robust indicators for burn mortality.²⁹ Age even as a single variable strongly predicts mortality in burns,³⁰ and in-hospital mortality in elderly burn patients is a function of age regardless of other comorbidities.³¹ In nonelderly patients, comorbidities such as preinjury human immunodeficiency virus (HIV), metastatic cancer, and kidney or liver disease may influence mortality and length of stay.³² A recent large database study of 68,661 burn patients found that the variables with the highest predictive value for mortality were age, %TBSA, inhalation injury, coexistent trauma, and pneumonia.³³

RESUSCITATION

A myriad of formulas exist for calculating fluid needs during burn resuscitation, suggesting that no one formula benefits all patients. The most commonly used formula, the Parkland or Baxter formula, consists of 3 to 4 mL/kg/% burn of lactated Ringer's, of which half is given during the first 8 hours after burn and the remaining half is given over the subsequent 16 hours. The concept behind continuous fluid requirements is simple. The burn (and/or inhalation injury) drives an inflammatory response that leads to capillary leak; as plasma leaks into the extravascular space, crystalloid administration maintains the intravascular volume. Therefore, if a patient receives a large fluid bolus in a prehospital setting or emergency department, that fluid has likely leaked into the interstitium and the patient still requires ongoing burn resuscitation according to the estimates. Continuation of fluid volumes should depend on the time since injury, urine output, and mean arterial pressure (MAP). As the leak closes, the patient will require less volume to maintain these two resuscitation endpoints. Children under 20 kg have the

additional requirement that they do not have sufficient glycogen stores to maintain an adequate glucose level in response to the inflammatory response. Specific pediatric formulas have been described, but the simplest approach is to deliver a weight-based maintenance IV fluid with glucose supplementation in addition to the calculated resuscitation fluid with lactated Ringer's.

It is important to remember that any formula for burn resuscitation is merely a guideline, and fluid must be titrated based on appropriate measures of adequate resuscitation. A number of parameters are widely used to gauge burn resuscitation, but the most common remain the simple outcomes of blood pressure and urine output. As in any critically ill patient, a target

4▶ MAP of 60 mmHg ensures optimal end-organ perfusion.

Goals for urine output should be 30 mL/h in adults and 1 to 1.5 mL/kg/h in pediatric patients. Because blood pressure and urine output may not correlate perfectly with true tissue perfusion, the search continues for other adjunctive parameters that may more accurately reflect adequate resuscitation. Some centers have found serum lactate to be a better predictor of mortality in severe burns,^{34,35} and others have found that base deficit predicts eventual organ dysfunction and mortality.^{36,37} Because burned patients with normal blood pressure and serum lactate levels may have compromised gastric mucosal perfusion, continuous measurement of mucosal pH with its logistical difficulties has garnered limited popularity.^{38,39} Invasive monitoring with pulmonary artery catheters typically results in significant excessive fluid administration without improved cardiac output or preload measurements; use of invasive monitoring seems to have variable effects on long-term outcomes.⁴⁰

Actual administered fluid volumes typically exceed volumes predicted by standard formulas.⁴¹ One survey of burn centers showed that 58% of patients end up getting more fluids than would be predicted by Baxter's formula.⁴² Comparison of modern-day patients with historical controls shows that over-resuscitation may be a relatively recent trend.⁴³ One theory is that increased opioid analgesic use results in peripheral vasodilation and hypotension and the need for greater volumes of bloused resuscitative fluids.⁴⁴ A classic study by Navar et al showed that burned patients with inhalation injury required an average of 5.76 mL/kg/% burn, vs. 3.98 mL/kg/% burn for patients without inhalation injury, and this has been corroborated by subsequent studies.^{45,46} Prolonged mechanical ventilation may also play a role in increased fluid needs.⁴⁷ A recent multicenter study found that age, weight, %TBSA, and intubation on admission were significant predictors of more fluid delivery during the resuscitation period. Those patients receiving higher fluid volumes were at increased risk of complications and death.⁴⁸ Common complications include abdominal compartment syndrome, extremity compartment syndrome, intraocular compartment syndrome, and pleural effusions. Monitoring bladder pressures can provide valuable information about development of intra-abdominal hypertension.

The use of colloid as part of the burn resuscitation has generated much interest over the years. In late resuscitation when the capillary leak has closed, colloid administration may decrease overall fluid volumes and potentially may decrease associated complications such as intra-abdominal hypertension.⁴⁹ However, albumin use has never been shown to improve outcomes in burn patients and has controversial effects on mortality in critically ill patients.^{50,51} Attempts to minimize fluid volumes in burn resuscitation have included study of hypertonic solutions, which appear to transiently decrease initial resuscitation volumes, with the downside of causing hyperchloremic acidosis.⁵²

Other adjuncts are being increasingly used during initial burn resuscitation. High-dose ascorbic acid (vitamin C) may decrease fluid volume requirements and ameliorate respiratory embarrassment during resuscitation.⁵³ Plasmapheresis may also decrease fluid requirements in patients who require higher volumes than predicted to maintain adequate urine output and MAP. It is postulated that plasmapheresis may filter out inflammatory mediators, thus decreasing ongoing vasodilation and capillary leak.⁵⁴

One recent adjunct that has found increasing utility in other surgical ICUs has been the application of bedside thoracic ultrasound.⁵⁵ Ultrasound offers the potential to make rapid, noninvasive assessments during acute changes in clinical condition. For burn patients, bedside ultrasonography may be indicated for evaluation of volume status, gross assessment of cardiac function, and diagnosis of pneumothorax. Determining patient cardiac function and volume status may guide fluid resuscitation. Cardiac function can be evaluated with three common heart views: the parasternal long axis, parasternal short axis, and apical four-chamber views.⁵⁶ Volume status can be estimated by examination of cardiac function, evaluation of the inferior vena cava (IVC) diameter, and changes with respiration. Ultrasound also allows timely diagnosis of pneumothorax.⁵⁷ A high-frequency probe with an adequate window between ribs permits identification of lung parenchyma against the chest wall. A pneumothorax appears as a transition on ultrasound between lung parenchyma, which has a heterogeneous appearance, and air, which has a hypoechoic appearance. Further studies are warranted to identify indications for the use of ultrasound in burned patients.

TRANSFUSION

The role of blood transfusion in critically injured patients has undergone a reevaluation in recent years.^{58,59} Blood transfusions are considered to be immunosuppressive, which is one explanation for the common responses seen to blood transfusions, such as increased infection and shorter time to recurrence after oncologic surgery.⁶⁰ A large multicenter study of blood transfusions in burn patients found that increased numbers of transfusions were associated with increased infections and higher mortality in burn patients, even when correcting for burn severity.⁶¹ A follow-up study implanting a restrictive transfusion policy in burned children showed that a hemoglobin threshold of 7 g/dL had no more adverse outcomes vs. a traditional transfusion trigger of 10 g/dL. In addition, costs incurred to the institution were significantly less.⁶² These data, in concert with other reported complications such as transfusion-related lung injury,⁶³ have led to recommendations that blood transfusions be used only when there is an apparent physiologic need. Attempts to minimize blood transfusion in nonburned critically ill patients have led to use of erythropoietin by some centers. However, burn patients often have elevated erythropoietin levels, and a randomized study in burn patients showed that recombinant human erythropoietin did not effectively prevent anemia or decrease the number of transfusions given.⁶⁴

INHALATION INJURY AND VENTILATOR MANAGEMENT

Inhalation injuries are commonly seen in tandem with burn injuries and are known to increase mortality in burned patients.⁶⁵ Smoke inhalation is present in as many as 35% of hospitalized burn patients and may triple the hospital stay compared to

isolated burn injuries.⁶⁶ The combination of burns, inhalation injury, and pneumonia increases mortality by up to 60% over burns alone.⁶⁷ Subsequent development of the adult respiratory distress syndrome (ARDS) is common in these patients and may be caused in part by recruitment of alveolar leukocytes with an enhanced endotoxin-activated cytokine response.⁶⁸ When ARDS complicates burns and inhalation injury, mortality approaches 66%; in one study, patients with burns $\geq 60\%$ TBSA in combination with inhalation injury and ARDS had 100% mortality.⁶⁹

Smoke inhalation causes injury in two ways: by direct heat injury to the upper airways and inhalation of combustion products into the lower airways. Direct injury to the upper airway causes airway swelling that typically leads to maximal edema in the first 24 to 48 hours after injury and often requires a short course of endotracheal intubation for airway protection. Combustion products found in smoke, most commonly from synthetic substances in structural fires, cause lower airway injury. These irritants cause direct mucosal injury, which in turn leads to mucosal sloughing, edema, reactive bronchoconstriction, and finally obstruction of the lower airways. Injury to both the epithelium and pulmonary alveolar macrophages causes release of prostaglandins, chemokines, and other inflammatory mediators; neutrophil migration; increased tracheobronchial blood flow; and finally increased capillary permeability. All of these components of acute lung injury increase the risk of pneumonia and ARDS following an inhalation injury.

The physiologic effects of smoke inhalation are numerous. Inhalation injury decreases lung compliance⁷⁰ and increases airway resistance work of breathing.⁷¹ Inhalation injury in the presence of burns also increases overall metabolic demands.⁷² The most common physiologic derangement seen with inhalation injury is increased fluid requirement during resuscitation. Since severe inhalation injury may result in mucosal sloughing with obstruction of smaller airways, bronchoscopy findings including carbon deposits, erythema, edema, bronchorrhea, and a hemorrhagic appearance may be useful for staging inhalation injury. Furthermore, bronchoalveolar lavage within 24 hours after an inhalation injury demonstrates a high rate of positive quantitative cultures,⁷³ suggesting that pneumonia develops soon after the acute lung injury. Because bronchoscopy is an invasive test, attempts have been made to utilize other diagnostic modalities, such as thoracic computed tomography (CT) scans⁷⁴ and xenon ventilation-perfusion scanning.⁷⁵ Decreased $\text{PaO}_2:\text{FiO}_2$ ratio (<200) on admission may not only predict inhalation injury but also indicate increased fluid needs more accurately than bronchoscopic grading of the severity of inhalation.⁷⁶

Treatment of inhalation injury consists primarily of supportive care. Aggressive pulmonary toilet and routine use of nebulized bronchodilators such as albuterol are recommended. Nebulized *N*-acetylcysteine is an antioxidant free radical scavenger designed to decrease the toxicity of high oxygen concentrations. Aerosolized heparin aims to prevent formation of fibrin plugs and decrease the formation of airway casts. These agents seem to improve pulmonary toilet but have no demonstrated effect on mortality.⁷⁷ Aerosolized tissue plasminogen activator⁷⁸ and recombinant human antithrombin⁷⁹ have shown promise in sheep models, but have not yet seen widespread clinical use. Administration of intrabronchial surfactant has been used as a salvage therapy in patients with severe burns and inhalation injury.⁸⁰ Inhaled nitric oxide may also be useful as a last effort in burn patients with severe lung injury who are failing other means of ventilatory support.⁸¹ The use of steroids has traditionally

been avoided due to worse outcomes in burn patients,⁸² but new promising data in late ARDS have prompted scientific review of steroid use.⁸³

New ventilator strategies have contributed to the improved mortality with ARDS. Although ARDS still contributes to mortality in burn patients, treatments have improved so that mortality is primarily from multisystem organ failure rather than isolated respiratory causes.⁸⁴ The ARDS Network Study finding that low tidal volume (6 cc/kg) or “lung-protective ventilation” had a 22% lower mortality than patients with traditional tidal volumes (12 cc/kg)⁸⁵ has dramatically changed the management of patients with acute lung injury. A similar approach had previously been shown to improve outcomes in pediatric burn patients.⁸⁶ In patients with refractory hypoxemia despite lung-protective ventilation, prone positioning may improve oxygenation but has not shown a definitive effect on mortality.⁸⁷ No specific studies have examined prone positioning in burned patients, and caution must be used in patients with facial burns who are already at risk for loss of the endotracheal tube. High-frequency percussive ventilation (HFPV) has shown early promise in patients with inhalation injury.⁸⁸ One study showed notable decreases in both morbidity and mortality with HFPV, especially in patients with burns less than 40% TBSA and inhalation injury.⁸⁹ A related technique is high-frequency oscillatory ventilation, which has been used primarily as a salvage modality in patients refractory to more conventional measures.⁹⁰ Extracorporeal membrane oxygenation (ECMO) is typically reserved for salvage situations, and experience with this modality is limited to small numbers of patients.⁹¹ A promising area of future study may be arteriovenous carbon dioxide removal, a technique that has proven superior to both low tidal volume ventilation and HFPV in a sheep model but has not yet transitioned from bench to bedside.⁹²

TREATMENT OF THE BURN WOUND

Multitudes of topical therapies exist for the treatment of burn wounds. Silver sulfadiazine is one of the most widely used in clinical practice. Silver sulfadiazine has a wide range of antimicrobial activity, primarily as prophylaxis against burn wound infections rather than treatment of existing infections. It has the added benefits of being inexpensive and easily applied and has soothing qualities. It is not significantly absorbed systemically and thus has minimal metabolic derangements. Silver sulfadiazine has a reputation for causing neutropenia, but this association is more likely due to neutrophil margination from the inflammatory response. True allergic reactions to the sulfa component of silver sulfadiazine are rare, and at-risk patients can have a small test patch applied to identify a burning sensation or rash. Silver sulfadiazine destroys skin grafts and is contraindicated on burns or donor sites in proximity to newly grafted areas. Also, silver sulfadiazine may retard epithelial migration in healing partial-thickness wounds.

Mafenide acetate, either in cream or solution form, is an effective topical antimicrobial. It is effective even in the presence of eschar and can be used in both treating and preventing wound infections; the solution formulation is an excellent antimicrobial for fresh skin grafts. Use of mafenide acetate may be limited by pain with application to partial-thickness burns. Mafenide is absorbed systemically, and a major side effect is metabolic acidosis resulting from carbonic anhydrase inhibition.

Silver nitrate has broad-spectrum antimicrobial activity as a topical solution. The solution used must be dilute (0.5%), and

prolonged topical application leads to electrolyte extravasation with resulting hyponatremia. A rare complication is methemoglobinemia. Although inexpensive, silver nitrate solution causes black stains, and laundry costs may offset any fiscal benefit to the hospital. Increasingly, Dakin's solution (0.5% sodium hypochlorite solution) is being used as an inexpensive topical antimicrobial.

For smaller burns or larger burns that are nearly healed, topical ointments such as bacitracin, neomycin, and polymyxin B can be used. These are also useful for superficial partial-thickness facial burns as they can be applied and left open to air without dressing coverage. Meshed skin grafts in which the interstices are nearly closed are another indication for use of these agents, preferably with greasy gauze to help retain the ointment in the affected area. All three have been reported to cause nephrotoxicity and should be used sparingly in large burns. The recent media fascination with methicillin-resistant *Staphylococcus aureus* (MRSA) has led to widespread use by community practitioners of mupirocin for new burns. Unless the patient has known risk factors for MRSA, mupirocin should only be used in culture-positive burn wound infections to prevent emergence of further resistance.

Silver-impregnated dressings such as Acticoat (Smith & Nephew, London, United Kingdom), Aquacel Ag (Convatec, Princeton, NJ), and Mepilex Ag (Mölnlycke Health Care US, LLC, Norcross, GA) are increasingly being used for donor sites, skin grafts, and partial-thickness burns. These may be more comfortable for the patient, reduce the number of dressing changes, and shorten hospital length of stay, but they do limit serial wound examinations. Biologic membranes such as Biobrane (Dow-Hickham, Sugarland, TX) provide a prolonged barrier under which wounds may heal. Because of the occlusive nature of these dressings, these are typically used only on fresh superficial partial-thickness burns that are clearly not contaminated.

NUTRITION

Nutritional support may be more important in patients with large burns than in any other patient population. Not only does adequate nutrition play a role in acute issues such as immune responsiveness, but the hypermetabolic response in burn injury may raise baseline metabolic rates by as much as 200%.⁹³ This can lead to catabolism of muscle proteins and decreased lean body mass that may delay functional recovery.⁹⁴ Early enteral feeding for patients with burns larger than 20% TBSA is safe and may reduce loss of lean body mass,⁹⁵ slow the hypermetabolic response,⁹⁶ and result in more efficient protein metabolism.⁹⁷ If the enteral feeds are started within the first few hours after admission, gastric ileus can be avoided. Adjuncts such as metoclopramide promote gastrointestinal motility; if other measures for gastric feeding are unsuccessful, advancing the tube into the small bowel with nasojejunal feeding can be attempted.⁹⁸ In endotracheally intubated patients, trips to the operating room do not necessitate holding enteral feedings.⁹⁹ Immune-modulating supplements such as glutamine may decrease infectious complications and mortality in burn patients,¹⁰⁰ likely via prevention of T-cell suppression in mesenteric lymph nodes.¹⁰¹

Calculating the appropriate caloric needs of the burn patient can be challenging. A commonly used formula in non-burned patients is the Harris-Benedict equation, which calculates caloric needs using factors such as gender, age, height, and weight. This formula uses an activity factor for specific injuries,

and for burns, the basal energy expenditure is multiplied by two. The Harris-Benedict equation may be inaccurate in burns of less than 40% TBSA, and in these patients, the Curreri formula may be more appropriate. This formula estimates caloric needs to be 25 kcal/kg/d plus 40 kcal/%TBSA/d. Indirect calorimetry can also be used to calculate resting energy expenditure, but in burn patients, a “metabolic cart” has not been documented to be more beneficial than the predictive equations.¹⁰² Titrating caloric needs closely is important, because overfeeding patients will lead to storage of fat instead of muscle anabolism.¹⁰³

Modifying the hypermetabolic response is an area of intense study with several recent findings. β -Blocker use in pediatric patients decreases heart rate and resting energy expenditure and abrogates protein catabolism, even in long-term use.¹⁰⁴ There may be benefits to β -blockade in adult patients,¹⁰⁵ and many centers use β -blockers routinely in the adult population with limited safety and efficacy data. The anabolic steroid oxandrolone has been extensively studied in pediatric patients as well, and has demonstrated improvements in lean body mass and bone density in severely burned children.¹⁰⁶ The weight gain and functional improvements seen with oxandrolone may persist even after stopping administration of the drug.¹⁰⁷ A recent double-blind, randomized study of oxandrolone showed decreased length of stay, improved hepatic protein synthesis, and no adverse effects on endocrine function, although the authors noted a rise in transaminases with unclear clinical significance.¹⁰⁸ Intensive insulin therapy in critically ill patients has shown benefit, presumably from avoidance of hyperglycemia.¹⁰⁹ However, in burn patients, the insulin itself may have a metabolic benefit, with improvements in lean body mass and amelioration of the inflammatory response to burn injury.^{110,111} Oral hypoglycemic agents such as metformin also help to avoid hyperglycemia and may contribute to prevention of muscle catabolism.¹¹²

COMPLICATIONS IN BURN CARE

There are several complications commonly associated with treatment of burn patients. Though not always avoidable, maintaining vigilance for typical complications and using appropriate techniques for prevention may limit the frequency and severity of complications. Ventilator-associated pneumonia, as in all critically ill patients, is a significant problem in burned patients. However, it is so common in patients with inhalation injury that a better nomenclature may be postinjury pneumonia. Unfortunately, commonly used scores in critical illness such as the Clinical Pulmonary Infection Score (CPIS) have not been shown to be reliable in burn patients. Quantitative bronchoscopic cultures in the setting of clinical suspicion of pneumonia should guide treatment of pneumonia.¹¹³ Simple measures such as elevating the head of the bed and maintaining excellent oral hygiene and pulmonary toilet are recommended to help decrease the risk of postinjury pneumonia. There is some question as to whether early tracheostomy decreases infectious morbidity in burn patients and whether it improves long-term outcomes. There do not seem to be any major differences in the rates of pneumonia with early tracheostomy, though there may be reduced development of subglottic stenosis compared with prolonged endotracheal intubation.^{114,115} Practical considerations such as protection of facial skin grafts may influence the decision for tracheostomy placement. One major consideration in deciding whether to perform a tracheostomy has been the presence of eschar at the insertion site, which complicates

tracheostomy site care and increases the risk of airway infection. Bedside percutaneous dilatational tracheostomy is a facile method for performing tracheostomy and is reported to be as safe as open tracheostomy in the burn population.¹¹⁶

Massive resuscitation of burned patients may lead to an abdominal compartment syndrome characterized by increased airway pressures with hypoventilation, and decreased urine output and hemodynamic compromise. Decompressive laparotomy is the standard of care for refractory abdominal compartment syndrome but carries an especially poor prognosis in burn patients.¹¹⁷ Adjunctive measures such as minimizing fluid, performing torso escharotomies, decreasing tidal volumes, and chemical paralysis should be initiated before resorting to decompressive laparotomy. Patients undergoing massive resuscitation also develop elevated intraocular pressures and may require lateral canthotomy.¹¹⁸

Deep vein thrombosis (DVT) has been commonly believed to be a rare phenomenon in burned patients, and there is a paucity of controlled studies regarding heparin prophylaxis in this population.¹¹⁹ However, recent data show that up to 25% of burn patients develop DVT, and fatal pulmonary emboli have been reported in burn patients.^{120,121} A large retrospective study in patients with routine prophylaxis found DVT in only 0.25% of patients and reported no bleeding complications.¹²² Thus, it appears that heparin prophylaxis is safe in burn patients and may help prevent thrombotic complications.

Unfortunately, the use of both prophylactic and therapeutic heparin may be associated with heparin-associated thrombocytopenia (HIT). One study of HIT in burn patients showed an incidence of 1.6% in heparinized burn patients. Thrombotic complications included DVT, pulmonary embolus, and even arterial thrombosis requiring limb amputation. Nonheparin anticoagulation for HIT commonly caused bleeding complications requiring transfusion.¹²³ Although rare, a high index of suspicion for HIT should be maintained in thrombocytopenic burn patients, particularly if the platelet counts drop at hospital days 7 to 10.

Burn patients often require central venous access for fluid resuscitation and hemodynamic monitoring. Because of the anatomic relation of their burns to commonly used access sites, burn patients may be at higher risk for catheter-related bloodstream infections. The 2009 Centers for Disease Control and Prevention National Healthcare Safety Network report (<http://www.cdc.gov/nhsn/dataStat.html>) indicates that American burn centers have higher infectious complication rates than any other ICUs. Because burn patients may commonly exhibit leukocytosis with a documented bloodstream infection, practice has been to rewire lines over a guide wire and to culture the catheter tip. However, this may increase the risk of catheter-related infections in burned patients, and a new site should be used if at all possible.¹²⁴

SURGERY

Full-thickness burns with a rigid eschar can form a tourniquet effect as the edema progresses, leading to compromised venous outflow and eventually arterial inflow. The resulting compartment syndrome is most common in circumferential extremity burns, but abdominal and thoracic compartment syndromes also occur. Warning signs of impending compartment syndrome may include paresthesias, pain, decreased capillary refill, and progression to loss of distal pulses; in an intubated patient,

the surgeon should anticipate the compartment syndrome and perform frequent neurovascular evaluations. Abdominal compartment syndrome should be suspected with decreased urine output, increased ventilator airway pressures, and hypotension. Hypoventilation, increased airway pressures, and hypotension may also characterize thoracic compartment syndrome. Escharotomies are rarely needed within the first 8 hours following injury and should not be performed unless indicated because of the terrible aesthetic sequelae. When indicated, they are usually performed at the bedside, preferably with electrocautery to minimize blood loss. Extremity incisions are made on the lateral and medial aspects of the limbs in an anatomic position and may extend onto thenar and hypothenar eminences of the hand. Digital escharotomies do not usually result in any meaningful salvage of functional tissue and are not recommended. Inadequate perfusion despite proper escharotomies may indicate the need for fasciotomy, but this procedure should not be routinely performed as part of the eschar release. Thoracic escharotomies should be placed along the anterior axillary lines with bilateral subcostal and subclavicular extensions. Extension of the anterior axillary incisions down the lateral abdomen typically will allow adequate release of abdominal eschar.

The strategy of early excision and grafting in burned patients revolutionized survival outcomes in burn care. Not only did it improve mortality, but early excision also decreased reconstruction surgery, hospital length of stay, and costs of care.^{125,126} Once the initial resuscitation is complete and the patient is hemodynamically stable, attention should be turned to excising the burn wound. Burn excision and wound coverage should ideally start within the first several days, and in larger burns, serial excisions can be performed as patient condition allows. Excision is performed with repeated tangential slices using a Watson or Goulian blade until viable, diffusely bleeding tissue remains. It is appropriate to leave healthy dermis, which will appear white with punctate areas of bleeding. Excision to fat or fascia may be necessary in deeper burns. The downside of tangential excision is a high blood loss, though this may be ameliorated using techniques such as instillation of an epinephrine tumescence solution underneath the burn. Pneumatic tourniquets are helpful in extremity burns, and compresses soaked in a dilute epinephrine solution are necessary adjuncts after excision. A fibrinogen and thrombin spray sealant (Tisseel Fibrin Sealant; Baxter, Deerfield, IL) also has beneficial effects on both hemostasis and graft adherence to the wound bed. The use of these techniques has markedly decreased the number of blood transfusions given during burn surgery.¹²⁷ For patients with clearly deep burns and concern for excessive blood loss, fascial excision may be employed. In this technique, electrocautery is used to excise the burned tissue and the underlying subcutaneous tissue down to muscle fascia. This technique markedly decreases blood loss but results in a cosmetically inferior appearance due to the loss of subcutaneous tissue. For excision of burns in difficult anatomic areas such as the face, eyelids, or hands, a pressurized water dissector may offer more precision but is time consuming, has a steep learning curve, and is expensive.¹²⁸

WOUND COVERAGE

Since full-thickness burns are impractical for most burn wounds, split-thickness sheet autografts harvested with a power dermatome make the most durable wound coverings and have a decent cosmetic appearance. In larger burns, meshed

autografted skin provides a larger area of wound coverage. This also allows drainage of blood and serous fluid to prevent accumulation under the skin graft with subsequent graft loss. Areas of cosmetic importance such as the face, neck, and hands should be grafted with nonmeshed sheet grafts to ensure optimal appearance and function. Unfortunately, even extensive meshing of skin grafts in patients with limited donor sites may not provide adequate amounts of skin. Options for temporary wound coverage include human cadaveric allograft, which is incorporated into the wound but is rejected by the immune system and must be eventually replaced. This allows temporary biologic wound coverage until donor sites heal enough so that they may be reharvested. Xenograft appears to function as well as allograft for temporary wound coverage and is considerably less expensive.

The search for a perfect permanent synthetic skin substitute remains elusive. Integra (Integra LifeSciences Corporation, Plainsboro, NJ) is a bilayer product with a porous collagen-chondroitin 6-sulphate inner layer that is attached to an outer silastic sheet, which helps prevent fluid loss and infection as the inner layer becomes vascularized, creating an artificial neodermis. At approximately 2 weeks after placement, the silastic layer can be removed and a thin autograft can be placed over the neodermis. This results in faster healing of the more superficial donor sites and seems to be associated with hypertrophic scarring and improved joint function.¹²⁹ Alloderm (LifeCell Corporation, The Woodlands, TX) is another dermal substitute consisting of cryopreserved acellular human dermis. This must also be used in combination with thin split-thickness skin grafts.¹³⁰

Epidermal skin substitutes such as cultured epithelial autografts are an option in patients with massive burns and very limited donor sites.¹³¹ Their clinical use has been limited by a long turnaround time for culturing, as well as the fragility of the cultured skin, which creates great difficulty with intraoperative handling and graft take. There are promising developments in skin culturing techniques and engineered skin development, but no other products are Food and Drug Administration approved and commercially available.¹³²

Thighs make convenient anatomic donor sites; they are easily harvested and relatively hidden from an aesthetic standpoint. The thicker skin of the back is useful in older patients, who have thinner skin elsewhere and may have difficulty with healing of donor sites. The buttocks are an excellent donor site in infants and toddlers; silver sulfadiazine can be applied to the donor site with a diaper as coverage. The scalp is also an excellent donor site; the skin is thick and the many hair follicles allow rapid healing, with the added advantage of being completely hidden once hair regrows. Epinephrine tumescence is necessary for harvesting the scalp, for both hemostasis of this hypervascular area and also to create a smooth contoured surface for harvesting.

The list of commonly used donor site dressings is long and includes simple transparent films to hydrocolloids, petrolatum gauzes, and silver-impregnated dressings. Donor sites close to fresh grafts may be dressed with a porous nonadherent gauze, and both the donors and grafts are soaked with an antimicrobial solution. Principals behind choosing a dressing should balance ease of care, comfort, infection control, and cost. The choice of donor site dressing is largely institution dependent, and few data support the clear superiority of any single treatment plan.

REHABILITATION

Rehabilitation is an integral part of the clinical care plan for the burn patient and should be initiated on admission. Immediate and ongoing physical and occupational therapy is mandatory to prevent functional loss. Patients who are unable to actively participate should have passive range of motion done at least twice a day. This includes patients with burns over joints, such as with hand burns. Patients should be taught exercises they can do themselves to maintain full range of motion. Patients with foot and extremity burns should be instructed to walk independently without crutches or other assistive devices to prevent extremity swelling, desensitize the burned areas, and prevent disuse atrophy; when patients are not ambulating, they must elevate the affected extremity to minimize swelling. If postoperative immobilization is used for graft protection, the graft should be evaluated early and at frequent intervals so that active exercise can be resumed at the earliest possible occasion. The transition to outpatient care should also include physical and occupational therapy, with introduction of exercises designed to accelerate return to activities of daily living as well as specific job-related tasks. Tight-fitting pressure garments provide vascular support in burns that are further along in the healing process. Whether they prevent hypertrophic scar formation has been long debated. However, they do provide vascular support that many patients find more comfortable.

Once patients have recovered from their acute burns, many face management of the hypertrophic burn scars. In patients with healed burns or donor sites, hypertrophic scar-related morbidity includes pruritus, erythema, pain, thickened tight skin, and even contractures. Within these scars, there is believed to be an increased inflammatory response that has increased neovascularization, abundant collagen production, and abnormal extracellular matrix structure. Treatment for these scars has included nonsurgical therapies such as compression garments, silicone gel sheeting, massage, physical therapy, and corticosteroid. Surgical excision and scar revision represent more invasive scar management approaches that are often necessary for functional and aesthetic recovery.

Laser-based therapies provide additional treatment options for symptomatic hypertrophic scars. Two of the most common ones are the pulsed dye laser (PDL) and the ablative carbon dioxide (CO₂) laser. The PDL causes photothermolysis of hemoglobin, resulting in coagulative necrosis.¹³³ It obliterates small capillaries close to the skin and has had success treating congenital, cutaneous vascular malformations. The CO₂ laser has been used for treatment of acne and recently has been gaining increasing acceptance for its use to treat hypertrophic burn scars.¹³⁴ It works by ablating microscopic columns of tissue to flatten scars and is also believed to stimulate matrix metalloproteinases and other signaling pathways to induce collagen reorganization. Lasers are believed to help with scar remodeling and collagen reorganization. Outpatient and office-based treatment sessions are tolerated well by most patients. There is wide practice variation on when to start therapy and the number of treatments, but the literature has general support for starting treatment at 6 to 12 months and offering three treatments. More research is needed to determine the full potential of laser therapy to provide burn survivors a less invasive treatment of hypertrophic scars with improved symptoms and quality of life.

Psychological rehabilitation is equally important in the burn patient. Depression, posttraumatic stress disorder, concerns about image, and anxiety about returning to society constitute

predictable barriers to progress in both the inpatient and outpatient setting. Psychological distress occurs in as many as 34% of burn patients and persists in severity long after discharge.¹³⁵ Despite this, many patients will be able to quickly return to work or school, and goals should be set accordingly. The return to school for pediatric patients is actually very prompt, averaging about 10 days after discharge. However, further study is needed to determine whether attendance and performance suffer despite early re-entry to school.¹³⁶ The involvement of clinical psychologists and psychiatrists is invaluable in providing guidance and coping techniques to lessen the significant psychological burden of burn injury.

PREVENTION

Despite many areas of progress in prevention, burns continue to be a common source of injury. Some successful initiatives have included community-based interventions targeting simple home safety measures. Smoke alarms are known to decrease mortality from structural fires, but not all homes are equipped with proper smoke alarms, particularly in low-income households. Mandatory smoke alarm installation via community initiatives can be successful, but seems to be contingent on close long-term follow-up to ensure proper maintenance and function.^{137,138} Regulation of hot water heater temperatures has had some success and may be even more effective in conjunction with community-based programs emphasizing education and in-home inspections.^{139,140}

RADIATION BURNS

Interest in mass burn casualty disaster planning invariably includes a discussion of radiation burns. The 1945 nuclear bombing on Hiroshima and Nagasaki provided several important lessons for healthcare providers. First, the proximity to the detonated bomb directly impacted mortality. The fatality rate at 0.6 miles from ground zero was 86%, decreased to 27% at 0.6 to 1.6 miles, and was 2% for patients 1.6 to 3.1 miles away. Over 122,338 individuals died in Hiroshima, and 68,000 of these deaths occurred in the first 20 days. Of the survivors, 79,130 people were injured and 118,613 remain uninjured. Estimates of the injuries at Hiroshima suggest that 90% of patients had burns, 83% sustained traumatic injuries, and 37% had radiation injuries.^{141,142}

The mechanism of the explosion explains how radioactive material is distributed. A 20-kiloton nuclear device generates 180 mph winds 0.8 miles from the epicenter. The explosion results in a direct pressure wave and an indirect wind drag. The direct pressure can destroy windows and buildings, rupture eardrums, and cause pulmonary contusions, pneumothoraces, and hemothoraces. Radiation travels linearly, resulting in varying degree of burns depending on the distance from ground zero and time of exposure. A fireball at detonation sends radioactive material into the air and follows wind patterns settling to the ground in a predictable pattern. Thermal injuries near ground zero result in 100% fatalities due to incineration.^{141,142}

Radioactive material results in both acute injury from immediate exposure and more prolonged injury from delayed exposure to radioactive fallout or contamination. When a 10-kiloton nuclear bomb is detonated, people at a distance 0.7 miles from ground zero absorb 4.5 Gy. At 60 days, the medial lethal radiation dose (LD₅₀) is 3.5 Sv; with aggressive medical

care, this dose might be doubled to nearly 7 Sv. To put this in context, radiation exposure from a diagnostic CT of the chest or abdomen is 5 mSv, and the average annual background absorbed radiation dose is 3.6 mSv. Radiation is known to impact several organ systems and result in several syndromes based on increasing exposure doses. These syndromes include hematologic (1–8 Sv exposure), gastrointestinal (8–30 Sv exposure), and cardiovascular/neurologic syndromes (>30 Sv exposure), with the latter two being nonsurvivable.^{141–143}

After initial evaluation and decontamination by removing clothing, a useful way to estimate exposure is by determining the time to emesis. Patients who do not experience emesis within 4 hours of exposure are unlikely to have severe clinical effects. Emesis within 2 hours suggests a dose of at least 3 Sv, and emesis within 1 hour suggests at least 4 Sv. The hematologic system follows a similar dose-dependent temporal pattern for predicting radiation exposure, mortality, and treatment. These have been determined based on the Armed Forces Radiobiology Research Institute's Biodosimetry Assessment Tool, which can be downloaded from www.afrii.usuhs.mil.

The combination of radiation exposure and burn wounds has the potential to increase mortality compared with traditional burns. Early closure of wounds before radiation depletes circulating lymphocytes may be needed for wound healing (which occurs within 48 hours). Also, in radiation injuries combined with burn or trauma, laboratory lymphocyte counts may be unreliable.^{141–144} A significant difference between burn/traumatic injuries and radiation injuries is that burn/traumatic injuries can result in higher mortality when not treated within hours.

Decontamination and triage are vital to maximize the number of survivors. Initial decontamination requires removal of clothing and washing wounds with water. Irrigation fluid should be collected to prevent radiation spread into the water supply. Work by many professional organizations, including the ABA, has focused on nationwide triage for disasters and will be vital to save as many lives as possible. Yet, it is likely that expectant or comfort care could be offered to more patients than typically seen in civilian hospitals, due to resource availability after the disaster.

FUTURE AREAS OF STUDY

It has long been anecdotally noted that two patients of similar ages and burn size may have very divergent responses to their burn injuries. Attention is being increasingly turned to identifying genetic differences among burn patients and how they affect response to injury. Specific allele variants have been linked with increased mortality in burned patients.¹⁴⁵ It may be that genetic differences may predispose burn patients to severe sepsis,¹⁴⁶ perhaps by downregulating the immune response.¹⁴⁷ The Inflammation and the Host Response to Injury trial was a prospective, multicenter, federally funded study that aimed to define specific genetic pathways that differ in the response to both burns and traumatic injury.¹⁴⁸ Blood and tissue samples from a strictly defined patient population were analyzed using gene arrays to determine whether differential expression in certain genetic pathways affects clinical outcomes.¹⁴⁹ Although data from this study are still being analyzed, some interesting findings suggest that sepsis, trauma, and burn patients share common gene expression patterns, starting early after injury. These genes can upregulate proinflammatory pathways as well as disrupt antigen presentation pathways. A better understanding of these common genomic responses may allow for the targeted treatment

of immunologic and signal pathways to help improve patient survival from burn injuries.

With the dramatic progress in improving survival following a major burn injury during the twentieth century, understanding and addressing functional and psychological outcomes is critical to the well-being of burn survivors. Since 1993, the National Institute of Disability and Rehabilitation Research has funded four burn model systems to identify long-term sequelae of burn injuries and to develop ways to improve outcomes for survivors. Ongoing outcome studies are crucial for dismantling barriers that our patients face in returning to their communities and to the workplace or to school.

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chapter

Wound Healing

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HISTORY OF WOUND HEALING

The earliest accounts of wound healing date back to about 2000 B.C., when the Sumerians employed two modes of treatment: a spiritual method consisting of incantations, and a physical method of applying poultice-like materials to the wound. The Egyptians were the first to differentiate between infected and diseased wounds compared to noninfected wounds. The 1650 B.C. Edwin Smith Surgical Papyrus, a copy of a much older document, describes at least 48 different types of wounds. A later document (Ebers Papyrus, 1550 B.C.) relates the use of concoctions containing honey (antibacterial properties), lint (absorbent properties), and grease (barrier) for treating wounds. These same properties are still considered essential in contemporary daily wound management.

The Greeks, equipped with the knowledge bequeathed by the Egyptians, went even further and classified wounds as acute or chronic in nature. Galen of Pergamum (120–201 A.D.), appointed as the doctor to the Roman gladiators, had an enormous number of wounds to deal with following gladiatorial combats. He emphasized the importance of maintaining a moist environment to ensure adequate healing. It took almost 19 centuries for this important concept to be proven scientifically, when it was shown that the epithelialization rate increases by 50% in a moist wound environment when compared to a dry wound environment.¹

The next major stride in the history of wound healing was the discovery of antiseptics and their importance in reducing wound infections. Ignaz Philipp Semmelweis, a Hungarian obstetrician (1818–1865), noted that the incidence of puerperal fever was much lower if medical students, following cadaver-dissection class and prior to attending childbirth, washed their hands with soap and hypochlorite. Louis Pasteur (1822–1895) was instrumental in dispelling the theory of spontaneous

generation of germs and proving that germs existed in and were always introduced from the environment. Joseph Lister probably made one of the most significant contributions to wound healing. On a visit to Glasgow, Scotland, Lister noted that some areas of the city's sewer system were less murky than the rest. He discovered that the water from pipes that were dumping waste containing carbolic acid (phenol) was clear. In 1865, Lister began soaking his surgical instruments in phenol and spraying the operating rooms, reducing the postoperative mortality rates from 50% to 15%. After attending an impressive lecture by Lister in 1876, Robert Wood Johnson left the meeting and began 10 years of research that would ultimately result in the production of an antiseptic dressing in the form of cotton gauze impregnated with iodoform. Since then, several other materials have been used to impregnate cotton gauze to achieve antiseptics.

The 1960s and 1970s led to the development of polymeric dressings. These polymeric dressings can be custom made to specific parameters, such as permeability to gases (occlusive vs. semiocclusive), varying degrees of absorbency, and different physical forms. Due to the ability to customize, the available range of materials that aid in wound care has grown exponentially to include an ever-expanding variety. Currently, the practice of wound healing encompasses manipulation and/or use of, among others, inflammatory cytokines, growth factors, and bioengineered tissue. It is the combination of all these modalities that enables optimal wound healing.

PHASES OF WOUND HEALING

As noted by John Hunter (1728–1793), a keen observer of biologic phenomena, “. . . the injury alone has in all cases a tendency to produce the disposition and the means of a cure.”² Normal wound healing follows a predictable pattern that can be divided into overlapping phases defined by characteristic

Key Points

- 1▶ Wound healing is a complex cellular and biochemical cascade that leads to restitution of integrity and function.
- 2▶ Although individual tissues may have unique healing characteristics, all tissues heal by similar mechanisms, and the process undergoes phases of inflammation, cellular migration, proliferation, matrix deposition, and remodeling.
- 3▶ Factors that impede normal healing include local, systemic, and technical conditions that the surgeon must take into account.
- 4▶ Clinically, excess healing can be as significant a problem as impaired healing; genetic, technical, and local factors play a major role.
- 5▶ Optimal outcome of acute wounds relies on complete evaluation of the patient and of the wound and application of best practices and techniques.

cellular populations and biochemical activities: (a) hemostasis and inflammation, (b) proliferation, and (c) maturation and remodeling. An approximate timeline of these events is depicted in Fig. 9-1. This sequence of events is fluid and overlapping, and in most circumstances spans the time from injury to resolution of acute wounds. All wounds need to progress through this series of cellular and biochemical events that

characterizes the phases of healing in order to successfully re-establish tissue integrity.

Hemostasis and Inflammation

Hemostasis precedes and initiates inflammation with the ensuing release of chemotactic factors from the wound site (Fig. 9-2A). Wounding by definition disrupts tissue integrity, leading to

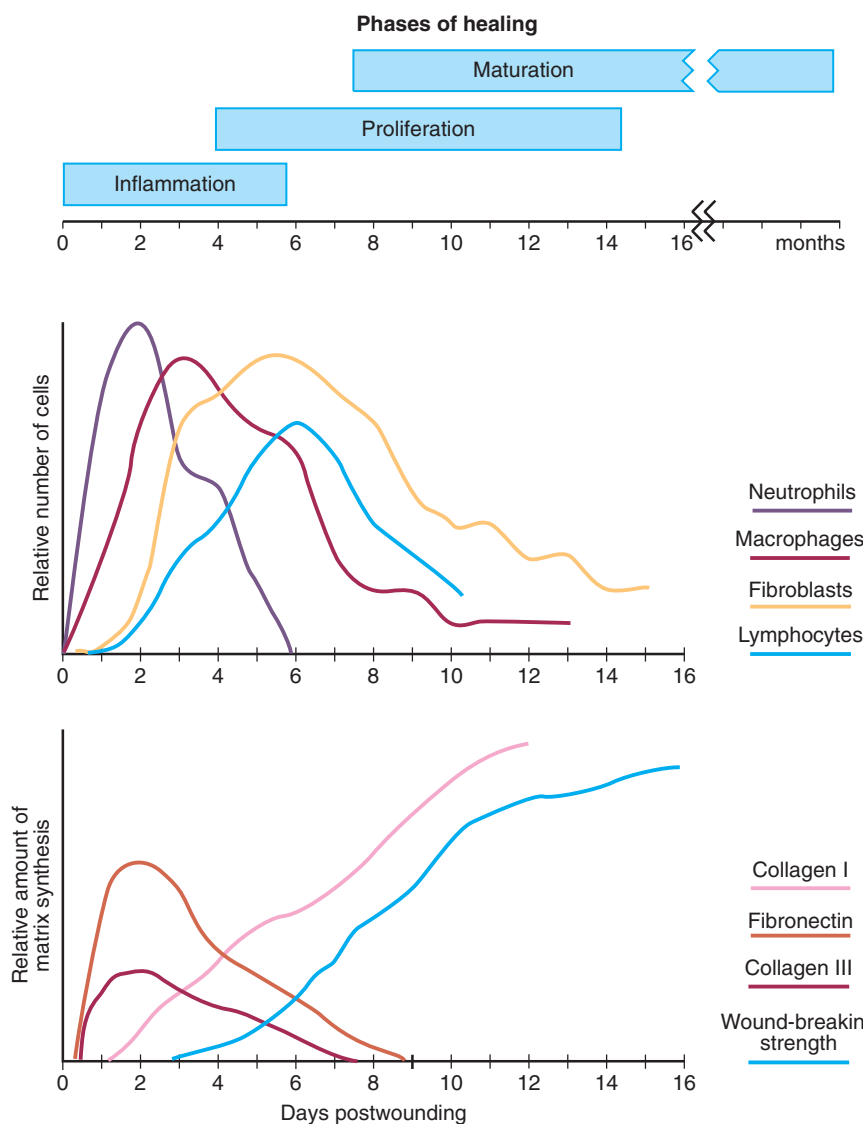


Figure 9-1. The cellular, biochemical, and mechanical phases of wound healing.

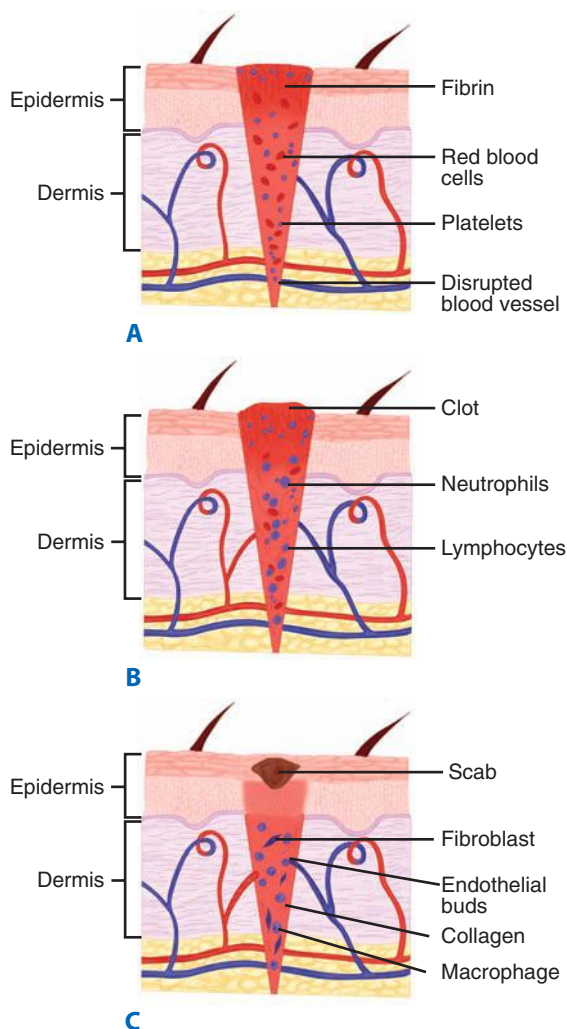


Figure 9-2. The phases of wound healing viewed histologically. **A.** The hemostatic/inflammatory phase. **B.** Latter inflammatory phases reflecting infiltration by mononuclear cells and lymphocytes. **C.** The proliferative phase, with associated angiogenesis and collagen synthesis.

division of blood vessels and direct exposure of extracellular matrix to platelets. Exposure of subendothelial collagen to platelets results in platelet aggregation, degranulation, and activation of the coagulation cascade. Platelet α granules release a number of wound-active substances, such as platelet-derived growth factor (PDGF), transforming growth factor- β (TGF- β), platelet-activating factor (PAF), fibronectin, and serotonin. In addition to achieving hemostasis, the fibrin clot serves as scaffolding for the migration into the wound of inflammatory cells such as polymorphonuclear leukocytes (PMNs, neutrophils) and monocytes.

Cellular infiltration after injury follows a characteristic, predetermined sequence (see Fig. 9-1). PMNs are the first infiltrating cells to enter the wound site, peaking at 24 to 48 hours. Increased vascular permeability, local prostaglandin release, and the presence of chemotactic substances such as complement factors, interleukin-1 (IL-1), tumor necrosis factor- α (TNF- α), TGF- β , platelet factor 4, or bacterial products all stimulate neutrophil migration.

The postulated primary role of neutrophils is phagocytosis of bacteria and tissue debris. PMNs are also a major source of cytokines early during inflammation, especially TNF- α ³ which may have a significant influence on subsequent angiogenesis and

collagen synthesis (see Fig. 9-2B). PMNs also release proteases such as collagenases, which participate in matrix and ground substance degradation in the early phase of wound healing. Other than their role in limiting infections, these cells do not appear to play a role in collagen deposition or acquisition of mechanical wound strength. On the contrary, neutrophil factors have been implicated in delaying the epithelial closure of wounds.⁴

The second population of inflammatory cells that invades the wound consists of macrophages, which are recognized as being essential to successful healing.⁵ Derived from circulating monocytes, macrophages achieve significant numbers in the wound by 48 to 96 hours postinjury and remain present until wound healing is complete.

Macrophages, like neutrophils, participate in wound débridement via phagocytosis and contribute to microbial stasis via oxygen radical and nitric oxide synthesis (see Fig. 9-2B,C). The macrophage's most pivotal function is activation and recruitment of other cells via mediators such as cytokines and growth factors, as well as directly by cell-cell interaction and intercellular adhesion molecules (ICAM). By releasing such mediators as TGF- β , vascular endothelial growth factor (VEGF), insulin-like growth factor (IGF), epithelial growth factor (EGF), and lactate, macrophages regulate cell proliferation, matrix synthesis, and angiogenesis.^{6,7} Macrophages also play a significant role in regulating angiogenesis and matrix deposition and remodeling (Table 9-1).

T lymphocytes comprise another population of inflammatory/immune cells that routinely invades the wound. Less numerous than macrophages, T-lymphocyte numbers peak at about 1 week postinjury and truly bridge the transition from the inflammatory to the proliferative phase of healing. Though known to be essential to wound healing, the role of lymphocytes in wound healing is not fully defined.⁸ A significant body of

Table 9-1

Macrophage activities during wound healing

ACTIVITY	MEDIATORS
Phagocytosis	Reactive oxygen species Nitric oxide
Débridement	Collagenase, elastase
Cell recruitment and activation	Growth factors: PDGF, TGF- β , EGF, IGF Cytokines: TNF- α , IL-1, IL-6 Fibronectin
Matrix synthesis	Growth factors: TGF- β , EGF, PDGF Cytokines: TNF- α , IL-1, IFN- γ Enzymes: arginase, collagenase Prostaglandins Nitric oxide
Angiogenesis	Growth factors: FGF, VEGF Cytokines: TNF- α Nitric oxide

EGF = epithelial growth factor; FGF = fibroblast growth factor; IGF = insulin-like growth factor; IFN- γ = interferon- γ ; IL = interleukin; PDGF = platelet-derived growth factor; TGF- β = transforming growth factor- β ; TNF- α = tumor necrosis factor- α ; VEGF = vascular endothelial growth factor.

data supports the hypothesis that T lymphocytes play an active role in the modulation of the wound environment. Depletion of most wound T lymphocytes decreases wound strength and collagen content,⁹ while selective depletion of the CD8⁺ suppressor subset of T lymphocytes enhances wound healing. However, depletion of the CD4⁺ helper subset has no effect.¹⁰ Lymphocytes also exert a downregulating effect on fibroblast collagen synthesis by cell-associated interferon (IFN)- γ , TNF- α , and IL-1. This effect is lost if the cells are physically separated, suggesting that extracellular matrix synthesis is regulated not only via soluble factors but also by direct cell-cell contact between lymphocytes and fibroblasts.¹¹

Proliferation

The proliferative phase is the second phase of wound healing and roughly spans days 4 through 12 (see Fig. 9-2C). It is during this phase that tissue continuity is re-established. Fibroblasts and endothelial cells are the last cell populations to infiltrate the healing wound, and the strongest chemotactic factor for fibroblasts is PDGF.^{12,13} Upon entering the wound environment, recruited fibroblasts first need to proliferate, and then become activated, to carry out their primary function of matrix synthesis remodeling. This activation is mediated mainly by the cytokines and growth factors released from wound macrophages.

Fibroblasts isolated from wounds synthesize more collagen than nonwound fibroblasts, they proliferate less, and they actively carry out matrix contraction. Although it is clear that the cytokine-rich wound environment plays a significant role in this phenotypic alteration and activation, the exact mediators are only partially characterized.^{14,15} Additionally, lactate, which accumulates in significant amounts in the wound environment over time (~10 mmol), is a potent regulator of collagen synthesis through a mechanism involving adenosine diphosphate (ADP)-ribosylation.^{16,17}

Endothelial cells also proliferate extensively during this phase of healing. These cells participate in the formation of new capillaries (angiogenesis), a process essential to successful wound healing. Endothelial cells migrate from intact venules close to the wound. Their migration, replication, and new capillary tubule formation is under the influence of such cytokines and growth factors as TNF- α , TGF- β , and VEGF. Although many cells produce VEGF, macrophages represent a major source in the healing wound, and VEGF receptors are located specifically on endothelial cells.^{18,19}

Matrix Synthesis

Biochemistry of Collagen. Collagen, the most abundant protein in the body, plays a critical role in the successful completion of adult wound healing. Its deposition, maturation, and subsequent remodeling are essential to the functional integrity of the wound.

Although there are at least 18 types of collagen described, the main ones of interest to wound repair are types I and III. Type I collagen is the major component of extracellular matrix in skin. Type III, which is also normally present in skin, becomes more prominent and important during the repair process.

Biochemically, each chain of collagen is composed of a glycine residue in every third position. The second position in the triplet is made up of proline or lysine during the translation process. The polypeptide chain that is translated from mRNA contains approximately 1000 amino acid residues and is called *procollagen*. Release of procollagen into the endoplasmic

reticulum results in the hydroxylation of proline to hydroxyproline and of lysine to hydroxylysine by specific hydroxylases (Fig. 9-3). Prolyl hydroxylase requires oxygen and iron as cofactors, α -ketoglutarate as co-substrate, and ascorbic acid (vitamin C) as an electron donor. In the endoplasmic reticulum, the procollagen chain is also glycosylated by the linking of galactose and glucose at specific hydroxylysine residues. These steps of hydroxylation and glycosylation alter the hydrogen bonding forces within the chain, imposing steric changes that force the procollagen chain to assume an α -helical configuration.

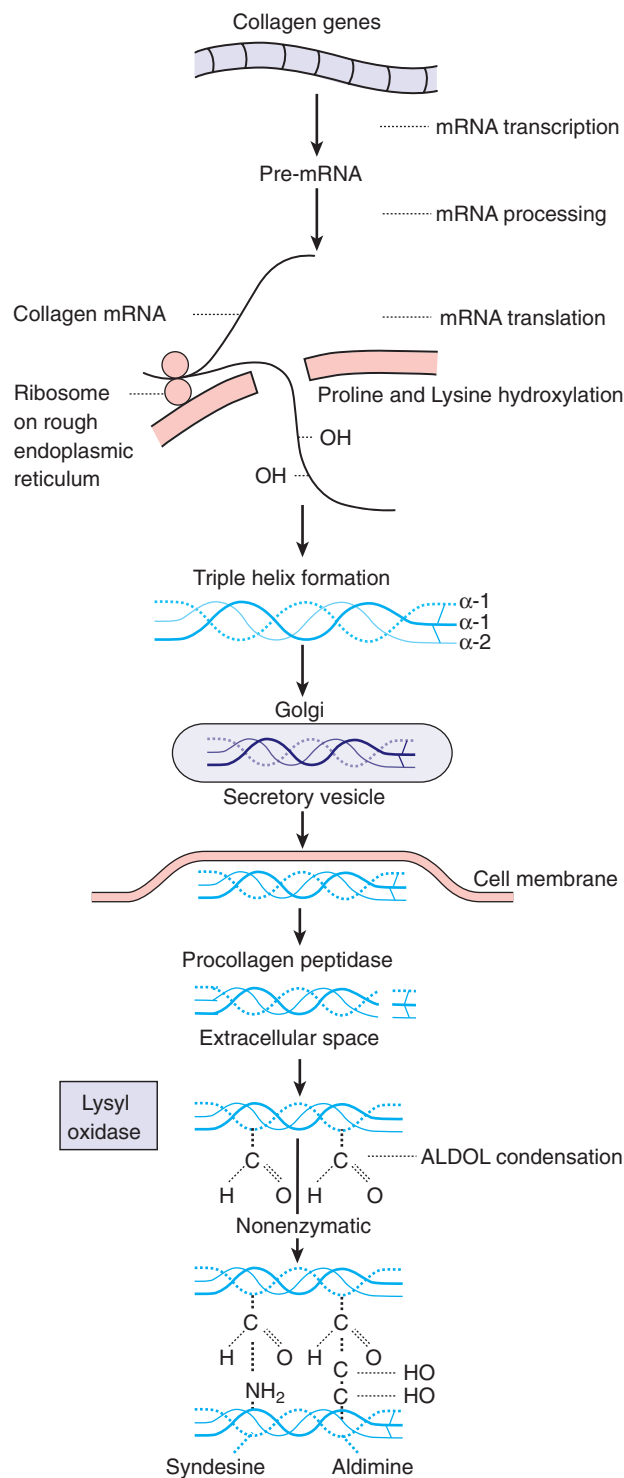


Figure 9-3. The steps of collagen synthesis. mRNA = messenger RNA.

Three α -helical chains entwine to form a right-handed superhelical structure called *procollagen*. At both ends, this structure contains nonhelical peptide domains called *registration peptides*. Although initially joined by weak, ionic bonds, the procollagen molecule becomes much stronger by the covalent cross-linking of lysine residues.

Extracellularly, the nonhelical registration peptides are cleaved by a procollagen peptidase, and the procollagen strands undergo further polymerization and cross-linking. The resulting collagen monomer is further polymerized and cross-linked by the formation of intra- and intermolecular covalent bonds.

Collagen synthesis, as well as posttranslational modifications, are highly dependent on systemic factors such as an adequate oxygen supply; the presence of sufficient nutrients (amino acids and carbohydrates) and cofactors (vitamins and trace metals); and the local wound environment (vascular supply and lack of infection). Addressing these factors and reversing nutritional deficiencies can optimize collagen synthesis and deposition.

Proteoglycan Synthesis. Glycosaminoglycans comprise a large portion of the “ground substance” that makes up granulation tissue. Rarely found free, they couple with proteins to form proteoglycans. The polysaccharide chain is made up of repeating disaccharide units composed of glucuronic or iduronic acid and a hexosamine, which is usually sulfated. The disaccharide composition of proteoglycans varies from about 10 units in the case of heparan sulfate to as much as 2000 units in the case of hyaluronic acid.

The major glycosaminoglycans present in wounds are dermatan and chondroitin sulfate. Fibroblasts synthesize these compounds, increasing their concentration greatly during the first 3 weeks of healing. The interaction between collagen and proteoglycans is being actively studied. It is thought that the assembly of collagen subunits into fibrils and fibers is dependent upon the lattice provided by the sulfated proteoglycans. Furthermore, it appears that the extent of sulfation is critical in determining the configuration of the collagen fibrils. As scar collagen is deposited, the proteoglycans are incorporated into the collagen scaffolding. However, with scar maturation and collagen remodeling, the content of proteoglycans gradually diminishes.

Maturation and Remodeling

The maturation and remodeling of the scar begins during the fibroplastic phase and is characterized by a reorganization of previously synthesized collagen. Collagen is broken down by matrix metalloproteinases (MMPs), and the net wound collagen content is the result of a balance between collagenolysis and collagen synthesis. There is a net shift toward collagen synthesis and eventually the re-establishment of extracellular matrix composed of a relatively acellular collagen-rich scar.

Wound strength and mechanical integrity in the fresh wound are determined by both the quantity and quality of the newly deposited collagen. The deposition of matrix at the wound site follows a characteristic pattern: fibronectin and collagen type III constitute the early matrix scaffolding; glycosaminoglycans and proteoglycans represent the next significant matrix components; and collagen type I is the final matrix. By several weeks postinjury, the amount of collagen in the wound reaches a plateau, but the tensile strength continues to increase for several more months.²⁰ Fibril formation and fibril cross-linking result in decreased collagen solubility, increased strength, and increased resistance to enzymatic degradation of the collagen matrix. Fibrillin, a glycoprotein secreted by fibroblasts, is essential for the formation of elastic fibers found in connective tissue.

Scar remodeling continues for many (6 to 12) months postinjury, gradually resulting in a mature, avascular, and acellular scar. The mechanical strength of the scar never achieves that of the uninjured tissue.

There is a constant turnover of collagen in the extracellular matrix, both in the healing wound as well as during normal tissue homeostasis. Collagenolysis is the result of collagenase activity, a class of MMPs that require activation. Both collagen synthesis and lysis are strictly controlled by cytokines and growth factors. Some factors affect both aspects of collagen remodeling. For example, TGF- β increases new collagen transcription and also decreases collagen breakdown by stimulating synthesis of tissue inhibitors of metalloproteinase.²¹ This balance of collagen deposition and degradation is the ultimate determinant of wound strength and integrity.

Epithelialization

While tissue integrity and strength are being re-established, the external barrier must also be restored. This process is characterized primarily by proliferation and migration of epithelial cells adjacent to the wound (Fig. 9-4). The process begins within 1 day of injury and is seen as thickening of the epidermis at the wound edge. Marginal basal cells at the edge of the wound lose their firm attachment to the underlying dermis, enlarge, and begin to migrate across the surface of the provisional matrix. Fixed basal cells in a zone near the cut edge undergo a series of rapid mitotic divisions, and these cells appear to migrate by moving over one another in a leapfrog fashion until the defect is covered.²²

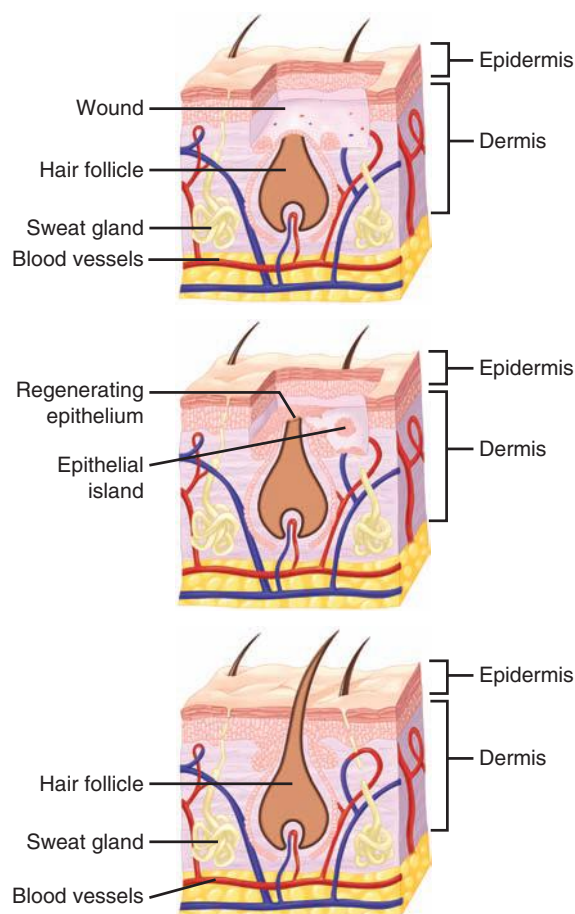


Figure 9-4. The healing by epithelialization of superficial cutaneous wounds.

Once the defect is bridged, the migrating epithelial cells lose their flattened appearance, become more columnar in shape, and increase their mitotic activity. Layering of the epithelium is re-established, and the surface layer eventually keratinizes.²³

Re-epithelialization is complete in less than 48 hours in the case of approximated incised wounds, but may take substantially longer in the case of larger wounds, where there is a significant epidermal/dermal defect. If only the epithelium and superficial dermis are damaged, such as occurs in split-thickness skin graft donor sites or in superficial second-degree burns, then repair consists primarily of re-epithelialization with minimal or no fibroplasia and granulation tissue formation. The stimuli for re-epithelialization remain incompletely defined; however, it appears that the process is mediated by a combination of a loss of contact inhibition; exposure to constituents of the extracellular matrix, particularly fibronectin; and cytokines produced by immune mononuclear cells.^{24,25} In particular EGF, TGF- β , basic fibroblast growth factor (bFGF), PDGF, and IGF-1 have been shown to promote epithelialization.

Role of Growth Factors in Normal Healing

Growth factors and cytokines are polypeptides produced in normal and wounded tissue that stimulate cellular migration, proliferation, and function. They often are named for the cells from which they were first derived (e.g., platelet-derived growth factor, PDGF) or for their initially identified function (e.g., fibroblast growth factor, FGF). These names are often misleading because growth factors have been demonstrated to have multiple functions. Most growth factors are extremely potent and produce significant effects in nanomolar concentrations.

They may act in an autocrine manner (where the growth factor acts on the cell producing it), a paracrine manner (by release into the extracellular environment, where it acts on the immediately neighboring cells), or in an endocrine manner (where the effect of the substance is distant to the site of release, and the substance is carried to the effector site through the blood stream). The timing of release may be as important as concentration in determining the effectiveness of growth factors. As these polypeptides exert their effects by cell-surface receptor binding, the appropriate receptor on the responding cells must be present at the time of release in order for the biologic effect to occur. Table 9-2 summarizes the principal growth factors found in healing wounds and their known effects on cells participating in the healing process. Growth factors have divergent actions on different cells; they can be chemoattractive to one cell type while stimulating replication of a different cell type. Little is known about the ratio of growth factor concentrations, which may be as important as the absolute concentration of individual growth factors.

Growth factors act on cells via surface receptor binding. Various receptor types have been described, such as ion channels, G-protein linked, or enzyme linked. The response elicited in the cell is usually one of phosphorylation or dephosphorylation of second-messenger molecules through the action of phosphatases or kinases, resulting in activation or deactivation of proteins in the cytosol or nucleus of the target cell. Phosphorylation of nuclear proteins is followed by the initiation of transcription of target genes.²⁶ The signal is stopped by internalization of the receptor-ligand complex.

Wound Contraction

All wounds undergo some degree of contraction. For wounds that do not have surgically approximated edges, the area of the wound will be decreased by this action (healing by secondary intention);

the shortening of the scar itself results in contracture. The myofibroblast has been postulated as being the major cell responsible for contraction, and it differs from the normal fibroblast in that it possesses a cytoskeletal structure. Typically this cell contains α -smooth muscle actin in thick bundles called *stress fibers*, giving myofibroblasts contractile capability.²⁷ The α -smooth muscle actin is undetectable until day 6, and then is increasingly expressed for the next 15 days of wound healing.²⁸ After 4 weeks, this expression fades and the cells are believed to undergo apoptosis.²⁹ A puzzling point is that the identification of myofibroblasts in the wound does not correspond directly to the initiation of wound contraction, which starts almost immediately after injury.

Fibroblasts placed in a collagen lattice in vitro actively move in the lattice and contract it without expressing stress fibers. It is postulated that the movement of cells with concomitant reorganization of the cytoskeleton is responsible for contraction.³⁰

HERITABLE DISEASES OF CONNECTIVE TISSUE

Heritable diseases of connective tissue consist of a group of generalized, genetically determined, primary disorders of one of the elements of connective tissue: collagen, elastin, or mucopolysaccharide. Five major types, Ehlers-Danlos syndrome, Marfan's syndrome, osteogenesis imperfecta, epidermolysis bullosa, and acrodermatitis enteropathica, will be discussed, as each provides unique challenges to the surgeon.

Ehlers-Danlos Syndrome

Ehlers-Danlos syndrome (EDS) is a group of 10 disorders that present as a defect in collagen formation. Over half of the affected patients manifest genetic defects encoding alpha chains of collagen type V, causing it to be either quantitatively or structurally defective. These changes lead to "classic" EDS with phenotypic findings that include thin, friable skin with prominent veins, easy bruising, poor wound healing, atrophic scar formation, recurrent hernias, and hyperextensible joints. Gastrointestinal problems include bleeding, hiatal hernia, intestinal diverticulae, and rectal prolapse. Small blood vessels are fragile, making suturing difficult during surgery. Large vessels may develop aneurysms, varicosities, or arteriovenous fistulas or may spontaneously rupture.³¹⁻³³ Table 9-3 presents a description of EDS subtypes including a recently recognized autosomal recessive form characterized by tenascin-X deficiency. The defect is a quantitative loss of protein, resulting in phenotypic changes similar to those observed in other types of EDS.

EDS must be considered in every child with recurrent hernias and coagulopathy, especially when accompanied by platelet abnormalities and low coagulation factor levels. Inguinal hernias in these children resemble those seen in adults. Great care should be taken to avoid tearing the skin and fascia. The transversalis fascia is thin, and the internal ring is greatly dilated. An adult-type repair with the use of mesh or felt may result in a lower incidence of recurrence.³⁴

The biochemical changes and phenotypic manifestation of the disease represent a major challenge to the surgeon. Dermal wounds should be closed in two layers, approximated with the sutures under tension, and the stitches should be left in place twice as long as usual. In addition, external fixation with adhesive tape can help reinforce the scar and prevent stretching.³⁵

Marfan's Syndrome

Patients with Marfan's syndrome have tall stature, arachnodactyly, lax ligaments, myopia, scoliosis, pectus excavatum, and aneurysm

Table 9-2

Growth factors participating in wound healing

GROWTH FACTOR	WOUND CELL ORIGIN	CELLULAR AND BIOLOGIC EFFECTS
PDGF	Platelets, macrophages, monocytes, smooth muscle cells, endothelial cells	Chemotaxis: fibroblasts, smooth muscle, monocytes, neutrophils Mitogenesis: fibroblasts, smooth muscle cells Stimulation of angiogenesis Stimulation of collagen synthesis Enhance re-epithelialization Modulate tissue remodeling
FGF	Fibroblasts, endothelial cells, keratinocytes, smooth muscle cells, chondrocytes	Stimulation of angiogenesis (by stimulation of endothelial cell proliferation and migration) Mitogenesis: mesoderm and neuroectoderm
HGF	Fibroblasts	Stimulates fibroblasts, keratinocytes, chondrocytes, myoblasts Suppresses inflammation, granulation tissue formation, angiogenesis, re-epithelialization
Keratinocyte growth factor	Keratinocytes, fibroblasts	Significant homology with FGF; stimulates keratinocytes
EGF	Platelets, macrophages, monocytes (also identified in salivary glands, duodenal glands, kidney, and lacrimal glands)	Stimulates proliferation and migration of all epithelial cell types
TGF- α	Keratinocytes, platelets, macrophages	Homology with EGF; binds to EGF receptor Mitogenic and chemotactic for epidermal and endothelial cells
TGF- β (three isoforms: β 1, β 2, β 3)	Platelets, T lymphocytes, macrophages, monocytes, neutrophils, fibroblasts, keratinocytes	Stimulates angiogenesis Stimulates leukocyte chemotaxis TGF- β 1 stimulates wound matrix production (fibronectin, collagen glycosaminoglycans); regulation of inflammation TGF- β 3 inhibits scar formation
Insulin-like growth factors (IGF-1, IGF-2)	Platelets (IGF-1 in high concentrations in liver; IGF-2 in high concentrations in fetal growth); likely the effector of growth hormone action	Promote protein/extracellular matrix synthesis Increase membrane glucose transport
Vascular endothelial growth factor	Macrophages, fibroblasts, endothelial cells, keratinocytes	Mitogen for endothelial cells (not fibroblasts) Stimulates angiogenesis Proinflammatory
IL-1	Macrophages, leukocytes, keratinocytes, fibroblasts	Proinflammatory Stimulates angiogenesis, re-epithelialization, tissue remodeling
IL-4	Leukocytes	Enhances collagen synthesis
IL-6	Fibroblasts, endothelial cells, macrophages, keratinocytes	Stimulates inflammation, angiogenesis, re-epithelialization, collagen deposition, tissue remodeling
Activin	Keratinocytes, fibroblasts	Stimulates granulation tissue formation, keratinocyte differentiation, re-epithelialization
Angiopoietin-1/-2 CX3CL1	Endothelial cells Macrophages, endothelial cells	Stimulates angiogenesis Stimulates inflammation, angiogenesis, collagen deposition
Granulocyte-macrophage colony-stimulating factor	Macrophage/monocytes, endothelial cells, fibroblasts	Stimulates macrophage differentiation/proliferation

CX3CL1 = chemokine (C-X3-C motif) ligand; EGF = epidermal growth factor; FGF = fibroblast growth factor; HGF = hepatocyte growth factor; IL = interleukin; PDGF = platelet-derived growth factor; TGF = transforming growth factor.

Table 9-3

Clinical, genetic, and biochemical aspects of Ehlers-Danlos subtypes

TYPE	CLINICAL FEATURES	INHERITANCE	BIOCHEMICAL DEFECT
I	Skin: soft, hyperextensible, easy bruising, fragile, atrophic scars; hypermobile joints; varicose veins; premature births	AD	Not known
II	Similar to type I, except less severe	AD	Not known
III	Skin: soft, not hyperextensible, normal scars; small and large joint hypermobility	AD	Not known
IV	Skin: thin, translucent, visible veins, normal scarring, no hyperextensibility; no joint hypermobility; arterial, bowel, and uterine rupture	AD	Type III collagen defect
V	Similar to type II	XLR	Not known
VI	Skin: hyperextensible, fragile, easy bruising; hypermobile joints; hypotonia; kyphoscoliosis	AR	Lysyl hydroxylase deficiency
VII	Skin: soft, mild hyperextensibility, no increased fragility; extremely lax joints with dislocations	AD	Type I collagen gene defect
VIII	Skin: soft, hyperextensible, easy bruising, abnormal scars with purple discoloration; hypermobile joints; generalized periodontitis	AD	Not known
IX	Skin: soft, lax; bladder diverticula and rupture; limited pronation and supination; broad clavicle; occipital horns	XLR	Lysyl oxidase defect with abnormal copper use
X	Similar to type II with abnormal clotting studies	AR	Fibronectin defect
TNx	Hypermobility joints, skin fragility	AR	Absence of tenascin X protein

AD = autosomal dominant; AR = autosomal recessive; XLR = X-linked recessive.

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of the ascending aorta. Patients who suffer from this syndrome also are prone to hernias. Surgical repair of a dissecting aneurysm is difficult, as the soft connective tissue fails to hold sutures. Skin may be hyperextensible but shows no delay in wound healing.^{36,37}

The genetic defect associated with Marfan's syndrome is a mutation in the *FBNI* gene, which encodes for fibrillin. Previously, it was thought that structural alteration of the microfibrillar system was responsible for the phenotypic changes seen with the disease. However, recent research indicates an intricate role that *FBNI* gene products play in TGF- β signaling. These extracellular matrix molecules normally bind and regulate TGF- β signaling; abnormal *FBNI* gene function may cause an increase in TGF- β signaling, particularly in the aortic wall.³⁸

Osteogenesis Imperfecta

Patients with osteogenesis imperfecta (OI) have brittle bones, osteopenia, low muscle mass, hernias, and ligament and joint laxity. OI is a result of a mutation in type I collagen. Mutations in prolidase, an enzyme responsible for cleaving c-terminal proline and hydroxyproline, may have a role in the disease. There are four major OI subtypes with mild to lethal manifestations. Patients experience dermal thinning and increased bruisability. Scarring is normal, and the skin is not hyperextensible. Surgery can be successful but difficult in these patients, as the bones fracture easily under minimal stress.^{31,34} Table 9-4 lists the various features associated with the clinical subtypes of OI.

Epidermolysis Bullosa

Epidermolysis bullosa (EB) is classified into four major subtypes: EB simplex, junctional EB, dystrophic EB, and Kindler's syndrome. The first three are determined by location in various

skin layers; the last can present as multiple blisters throughout different layers of skin. There are identified genetic defects for each subtype, but the overall phenotype is remarkably similar. The disease manifestations include impairment in tissue adhesion within the epidermis, basement membrane, or dermis, resulting in tissue separation and blistering with minimal trauma. Characteristic features of EB are blistering and ulceration. The recessively inherited dystrophic type is characterized by defects in the *COL7A1* gene, encoding type 7 collagen, important for connecting the epidermis to the dermis, and therefore phenotypically resulting in blistering.³⁹ Management of nonhealing

Table 9-4

Osteogenesis imperfecta: clinical and genetic features

TYPE	CLINICAL FEATURES	INHERITANCE
I	Mild bone fragility, blue sclera	Dominant
II	"Prenatal lethal"; crumpled long bones, thin ribs, dark blue sclera	Dominant
III	Progressively deforming; multiple fractures; early loss of ambulation	Dominant/recessive
IV	Mild to moderate bone fragility; normal or gray sclera; mild short stature	Dominant

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wounds in patients with EB is a challenge, as their nutritional status is compromised because of oral erosions and esophageal obstruction. Surgical interventions include esophageal dilatation and gastrostomy tube placement. Dermal incisions must be meticulously placed to avoid further trauma to skin.^{34,40} The skin requires nonadhesive pads covered by a “bulky” dressing to avoid blistering.

Acrodermatitis Enteropathica

Acrodermatitis enteropathica (AE) is an autosomal recessive disease of children that causes an inability to absorb sufficient zinc from breast milk or food. The AE mutation affects zinc uptake in the intestine by preventing zinc from binding to the cell surface and its translocation into the cell. Recently, the genetic defect has been localized on chromosome 8q24.3 identified as the *SLC39A4* gene, expressed in the intestinal lumen and upregulated based on zinc stores.⁴¹ Zinc deficiency is associated with impaired granulation tissue formation, as zinc is a necessary cofactor for DNA polymerase and reverse transcriptase, and its deficiency may impair healing due to inhibition of cell proliferation.

AE is characterized by impaired wound healing as well as erythematous pustular dermatitis involving the extremities and the areas around the bodily orifices. Diagnosis is confirmed by the presence of an abnormally low blood zinc level (>100 mg/dL). Oral supplementation with 100 to 400 mg zinc sulfate orally per day is curative for impaired healing.^{42,43}

HEALING IN SPECIFIC TISSUES

Gastrointestinal Tract

Healing of full-thickness injury to the gastrointestinal (GI) tract remains an unresolved clinical issue. Healing of full-thickness GI wounds begins with a surgical or mechanical reapposition of the bowel ends, which is most often the initial step in the repair process. Sutures or staples are principally used, although various other means such as buttons, plastic tubes, and various wrappings have been attempted with variable success. Failure of healing results in dehiscence, leaks, and fistulas, which carry significant morbidity and mortality. Conversely, excessive healing can be just as troublesome, resulting in stricture formation and stenosis of the lumen. Repair of the GI tract is vital to restoring the integrity of the luminal structure and to the resumption of motor, absorptive, and barrier functions.

The gross anatomic features of the GI tract are remarkably constant throughout most of its length. Within the lumen, the epithelium is supported by the lamina propria and underlying muscularis mucosa. The submucosa lies radially and circumferentially outside of these layers, is comprised of abundant collagenous and elastic fibers, and supports neural and vascular structures. Further toward the peritoneal surface of the bowel are the inner and outer muscle layers and ultimately a peritoneal extension, the serosa. The submucosa is the layer that imparts the greatest tensile strength and greatest suture-holding capacity, a characteristic that should be kept in mind during surgical repair of the GI tract. Additionally, serosal healing is essential for quickly achieving a watertight seal from the luminal side of the bowel. The importance of the serosa is underscored by the significantly higher rates of anastomotic failure observed clinically in segments of bowel that are extraperitoneal and lack serosa (i.e., the esophagus and rectum).

Injuries to all parts of the GI tract undergo the same sequence of healing as cutaneous wounds. However, there are some significant differences (Table 9-5). Mesothelial (serosal) and mucosal healing can occur without scarring. The early integrity of the anastomosis is dependent on formation of a fibrin seal on the serosal side, which achieves watertightness, and on the suture-holding capacity of the intestinal wall, particularly the submucosal layer. There is a significant decrease in marginal strength during the first week due to an early and marked collagenolysis. The lysis of collagen is carried out by collagenase derived from neutrophils, macrophages, and intraluminal bacteria. Recently, it has been shown that strains of *Pseudomonas aeruginosa* undergo phenotypic shifts characterized by higher collagenase secretion in an injured/anastomosed bowel environment.⁴⁴ Collagenase activity occurs early in the healing process, and during the first 3 to 5 days, collagen breakdown far exceeds collagen synthesis. The integrity of the anastomosis represents equilibrium between collagen lysis, which occurs early, and collagen synthesis, which takes a few days to initiate (Fig. 9-5). Collagenase is expressed postinjury in all segments of the GI tract, but it is much more marked in the colon compared to the small bowel. Collagen synthesis in the GI tract is carried out by both fibroblasts and smooth muscle cells. Colon fibroblasts produce greater amounts of collagen than skin fibroblasts, reflecting different phenotypic features, as well as different responses to cytokines and growth factors among these different fibroblast populations. Ultimate anastomotic strength is not always related to the absolute amount of collagen, and the structure and arrangement of the collagen matrix may be more important.⁴⁵

Technical Considerations. Traditional teaching holds that in order for an anastomosis to heal without complications it must be tension-free, have an adequate blood supply, receive adequate nutrition, and be free of sepsis. Although sound principles for all wound healing, there are several considerations unique to anastomotic healing. From a technical viewpoint, the ideal method of suturing two ends of bowel together has not yet been identified. Although debate exists concerning methods of creating an anastomosis, clinically there has been no convincing evidence that a given technique has any advantage over another (i.e., hand-sutured vs. stapled, continuous vs. interrupted sutures, absorbable vs. nonabsorbable sutures, or single- vs. two-layer closure). A recent meta-analysis revealed that stapled ileocolic anastomoses have fewer leak rates than hand-constructed ones, but no data on colo-colic or small bowel anastomoses have been offered yet.⁴⁶ It is known, however, that hand-sutured everting anastomoses are at greater risk of leakage and cause greater adhesion formation, but have a lower incidence of stenosis. Because no overall definite superiority of any one method exists, it is recommended that surgeons be familiar with several techniques and apply them as circumstances dictate.

The amount of intravenous fluid administered perioperatively affects many aspects of recovery from colonic surgery; experimental and clinical data show that anastomotic healing may be adversely affected by overzealous fluid administration, which results in fluid accumulation in the third space, increased abdominal pressure, and tissue edema, all of which can compromise blood flow in the small vessels at the healing edge.^{47,48}

Bone

Following any type of injury to bone, several changes take place at the site of injury to restore structural and functional integrity. Most of the phases of healing resemble those observed

Table 9-5

Comparison of wound healing in the gastrointestinal tract and skin

		GI TRACT	SKIN
Wound environment	pH	Varies throughout GI tract in accordance with local exocrine secretions	Usually constant except during sepsis or local infection
	Microorganisms	Aerobic and anaerobic, especially in the colon and rectum; problematic if they contaminate the peritoneal cavity	Skin commensals rarely cause problems; infection usually results from exogenous contamination or hematogenous spread
	Shear stress	Intraluminal bulk transit and peristalsis exert distracting forces on the anastomosis	Skeletal movements may stress the suture line but pain usually acts as a protective mechanism preventing excess movement
	Tissue oxygenation	Dependent on intact vascular supply and neocapillary formation	Circulatory transport of oxygen as well as diffusion
Collagen synthesis	Cell type	Fibroblasts and smooth muscle cells	Fibroblasts
	Lathyrogens	D-Penicillamine has no effect on collagen cross-linking	Significant inhibition of cross-linking with decreased wound strength
	Steroids	Contradictory evidence exists concerning their negative effect on GI healing; increased abscess in the anastomotic line may play a significant role	Significant decrease in collagen accumulation
Collagenase activity	—	Increased presence throughout GI tract after transection and reanastomosis; during sepsis excess enzyme may promote dehiscence by decreasing suture-holding capacity of tissue	Not as significant a role in cutaneous wounds
Wound strength	—	Rapid recovery to preoperative level.	Less rapid than GI tissue
Scar formation	Age	Definite scarring seen in fetal wound sites	Usually heals without scar formation in the fetus

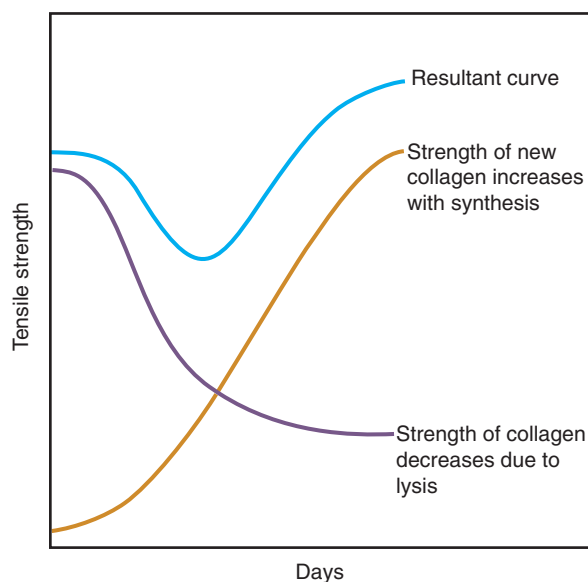


Figure 9-5. Diagrammatic representation of the concept of GI wound healing as a fine balance between collagen synthesis and collagenolysis. The “weak” period when collagenolysis exceeds collagen synthesis can be prolonged or exacerbated by any factors that upset the equilibrium. (Reproduced with permission from Hunt TK, Van Winkle W Jr. *Wound healing: normal repair*. In: Dunphy JE, ed. *Fundamentals of Wound Management in Surgery*. New York: Chirurgecom, Inc.; 1976:29.)

in dermal healing, but some notable individual characteristics apply to bone injuries. The initial stage of hematoma formation consists of an accumulation of blood at the fracture site, which also contains devitalized soft tissue, dead bone, and necrotic marrow. The next stage accomplishes the liquefaction and degradation of nonviable products at the fracture site. The normal bone adjacent to the injury site can then undergo revascularization, with new blood vessels growing into the fracture site. This is similar to the formation of granulation tissue in soft tissue. The symptoms associated with this stage are characteristic of inflammation, with clinical evidence of swelling and erythema.

Three to 4 days following injury, soft tissue forms a bridge between the fractured bone segments in the next stage (soft callus stage). This soft tissue is deposited where neovascularization has taken place and serves as an internal splint, preventing damage to the newly laid blood vessels and achieving a fibrocartilaginous union. The soft callus is formed externally along the bone shaft and internally within the marrow cavity. Clinically, this phase is characterized by the end of pain and inflammatory signs.

The next phase (hard callus stage) consists of mineralization of the soft callus and conversion to bone. This may take up to 2 to 3 months and leads to complete bony union. The bone is now considered strong enough to allow weight bearing and will appear healed on radiographs. This stage is followed by the remodeling phase, in which the excessive callus is reabsorbed and the marrow cavity is recanalized. This remodeling allows for the correct transmission of forces and restores the contours of the bone.

As in dermal healing, the process of osseous union is mediated by soluble growth factors and cytokines. The most extensively studied group is the bone morphogenic proteins (BMPs), which belong to the TGF- β superfamily. By stimulating the differentiation of mesenchymal cells into chondroblasts and osteoblasts, BMPs directly affect bone and cartilage repair. Other growth factors such as PDGF, TGF- β , TNF- α , and bFGF also participate in bony repair by mediating the inflammatory and proliferative phases of healing.

Cartilage

Cartilage consists of cells (chondrocytes) surrounded by an extracellular matrix made up of several proteoglycans, collagen fibers, and water. Unlike bone, cartilage is very avascular and depends on diffusion for transmittal of nutrients across the matrix. Additionally, the hypervascular perichondrium contributes substantially to the nutrition of the cartilage. Therefore, injuries to cartilage may be associated with permanent defects due to the meager and tenuous blood supply.

The healing response of cartilage depends on the depth of injury. In a superficial injury, there is disruption of the proteoglycan matrix and injury to the chondrocytes. There is no inflammatory response, but an increase in synthesis of proteoglycan and collagen dependent entirely on the chondrocyte. Unfortunately, the healing power of cartilage is often inadequate, and overall regeneration is incomplete. Therefore, superficial cartilage injuries are slow to heal and often result in persistent structural defects.

In contrast to superficial injuries, deep injuries involve the underlying bone and soft tissue. This leads to the exposure of vascular channels of the surrounding damaged tissue that may help in the formation of granulation tissue. Hemorrhage allows for the initiation of the inflammatory response and the subsequent mediator activation of cellular function for repair. As the granulation tissue is laid down, fibroblasts migrate toward the wound and synthesize fibrous tissue that undergoes chondrification. Gradually, hyaline cartilage is formed, which restores the structural and functional integrity of the injured site.

Tendon

Tendons and ligaments are specialized structures that link muscle and bone, and bone and bone, respectively. They consist of parallel bundles of collagen interspersed with spindle cells. Tendons and ligaments can be subjected to a variety of injuries, such as laceration, rupture, and contusion. Due to the mobility of the underlying bone or muscles, the damaged ends usually separate. Tendon and ligament healing progresses in a similar fashion as in other areas of the body (i.e., through hematoma formation, organization, laying down of reparative tissue, and scar formation). Matrix is characterized by accumulation of type I and III collagen along with increased water, DNA, and glycosaminoglycan content. As the collagen fibers are organized, transmission of forces across the damaged portion can occur. Restoration of the mechanical integrity may never be equal to that of the undamaged tendon.

Tendon vasculature has a clear effect on healing. Hypovascular tendons tend to heal with less motion and more scar formation than tendons with better blood supply. The specialized cells, tenocytes, are metabolically very active and retain a large regenerative potential, even in the absence of vascularity. Cells on the tendon surface are identical to those within the sheath and play a role in tendon healing as well.

Nerve

Nerve injuries are very common, with an estimated 200,000 repairs performed every year in the United States. Peripheral nerves are a complex arrangement of axons, nonneuronal cells, and extracellular elements. There are three types of nerve injuries: neurapraxia (focal demyelination), axonotmesis (interruption of axonal continuity but preservation of Schwann cell basal lamina), and neurotmesis (complete transection). Following all types of injury, the nerve ends progress through a predictable pattern of changes involving three crucial steps: (a) survival of axonal cell bodies; (b) regeneration of axons that grow across the transected nerve to reach the distal stump; and (c) migration and connection of the regenerating nerve ends to the appropriate nerve ends or organ targets.

Phagocytes remove the degenerating axons and myelin sheath from the distal stump (Wallerian degeneration). Regenerating axonal sprouts extend from the proximal stump and probe the distal stump and the surrounding tissues. Schwann cells ensheath and help in remyelinating the regenerating axons. Functional units are formed when the regenerating axons connect with the appropriate end targets. Several factors play a role in nerve healing, such as growth factors, cell adhesion molecules, and nonneuronal cells and receptors. Growth factors include nerve growth factor, brain-derived neurotrophic factor, basic and acidic fibroblastic growth factors, and neuroleukin. Cell adhesion molecules involved in nerve healing include nerve adhesion molecule, neuron-glia adhesion molecule, myelin adhesion glycoprotein, and N-cadherin. This complex interplay of growth factors and adhesion molecules helps in nerve regeneration.

Fetal Wound Healing

The main characteristic that distinguishes the healing of fetal wounds from that of adult wounds is the lack of scar formation. Understanding how fetal wounds achieve integrity without evidence of scarring holds promise for the possible manipulation of unwanted fibrosis or excessive scar formation in adults.

Although early fetal healing is characterized by the absence of scarring and resembles tissue regeneration, there is a phase of transition during gestational life when a more adult-like healing pattern emerges. This so-called “transition wound” occurs at the beginning of the third trimester, and during this period, there is scarless healing; however, there is a loss of the ability to regenerate skin appendages.⁴⁹ Eventually a classic, adult-patterned healing with scar formation occurs exclusively, although overall healing continues to be faster than in adults.

There are a number of characteristics that may influence the differences between fetal and adult wounds. These include wound environment, inflammatory responses, differential growth factor profiles, and wound matrix.

Wound Environment. The fetus is bathed in a sterile, temperature-stable fluid environment, although this alone does not explain the observed differences. Experiments have demonstrated that scarless healing may occur outside of the amniotic fluid environment, and conversely, scars can form in utero.^{50,51}

Inflammation. The extent and robustness of the inflammatory response correlates directly with the amount of scar formation in all healing wounds. Reduced fetal inflammation due to the immaturity of the fetal immune system may partially explain the lack of scarring observed. Not only is the fetus neutropenic, but fetal wounds contain lower numbers of PMNs and macrophages.⁵²

Growth Factors. Fetal wounds are notable for the absence of TGF- β , which may have a significant role in scarring. Conversely, blocking TGF- β 1 or TGF- β 2 using neutralizing antibodies considerably reduces scar formation in adult wounds. Exogenous application of TGF- β 3 downregulates TGF- β 1 and TGF- β 2 levels at the wound site with a resultant reduction in scarring.⁵³ Thus, the balance between the concentration and/or activity of TGF- β isoforms may be important for regulating scar production.

Wound Matrix. The fetal wound is characterized by excessive and extended hyaluronic acid production, a high-molecular-weight glycosaminoglycan that is produced primarily by fibroblasts. Although adult wounds also produce hyaluronic acid, its synthesis is sustained only in the fetal wound. Components of amniotic fluid, most specifically fetal urine, have a unique ability to stimulate hyaluronic acid production.⁵⁴ Fetal fibroblasts produce more collagen than adult fibroblasts, and the increased level of hyaluronic acid may aid in the orderly organization of collagen. As a result of these findings, hyaluronic acid is used topically to enhance healing and to inhibit postoperative adhesion formation.⁵⁵ The collagen pattern of fetal wounds is reticular in nature and resembles surrounding tissue, while adult patterns express large bundles of parallel collagen fibrils oriented perpendicular to the surface.⁵⁶

CLASSIFICATION OF WOUNDS

Wounds are classified as either acute or chronic. Acute wounds heal in a predictable manner and time frame. The process occurs with few, if any, complications, and the end result is a well-healed wound. Surgical wounds can heal in several ways. An incised wound that is clean and closed by sutures is said to heal by primary intention. Often, because of bacterial contamination or tissue loss, a wound will be left open to heal by granulation tissue formation and contraction; this constitutes healing by secondary intention. Delayed primary closure, or healing by tertiary intention, represents a combination of the first two, consisting of the placement of sutures, allowing the wound to stay open for a few days, and the subsequent closure of the sutures (Fig. 9-6).

The healing spectrum of acute wounds is broad (Fig. 9-7). In examining the acquisition of mechanical integrity and strength during healing, the normal process is characterized by a constant and continual increase that reaches a plateau at some point postinjury. Wounds with delayed healing are characterized by decreased wound-breaking strength in comparison to wounds that heal at a normal rate; however, they eventually achieve the same integrity and strength as wounds that heal normally. Conditions such as nutritional deficiencies, infections, or severe trauma cause delayed healing, which reverts to normal with correction of the underlying pathophysiology. Impaired healing is characterized by a failure to achieve mechanical strength equivalent to normally healed wounds. Patients with compromised immune systems such as those with diabetes, chronic steroid usage, or tissues damaged by radiotherapy are prone to this type of impaired healing. The surgeon must be aware of these situations and exercise great care in the placement of incision and suture selection, postoperative care, and adjunctive therapy to maximize the chances of healing without supervening complications.

Normal healing is affected by both systemic and local factors (Table 9-6). The clinician must be familiar with these factors and should attempt to counteract their deleterious effects. Complications occurring in wounds with higher risk can lead to failure of healing or the development of chronic, nonhealing wounds.

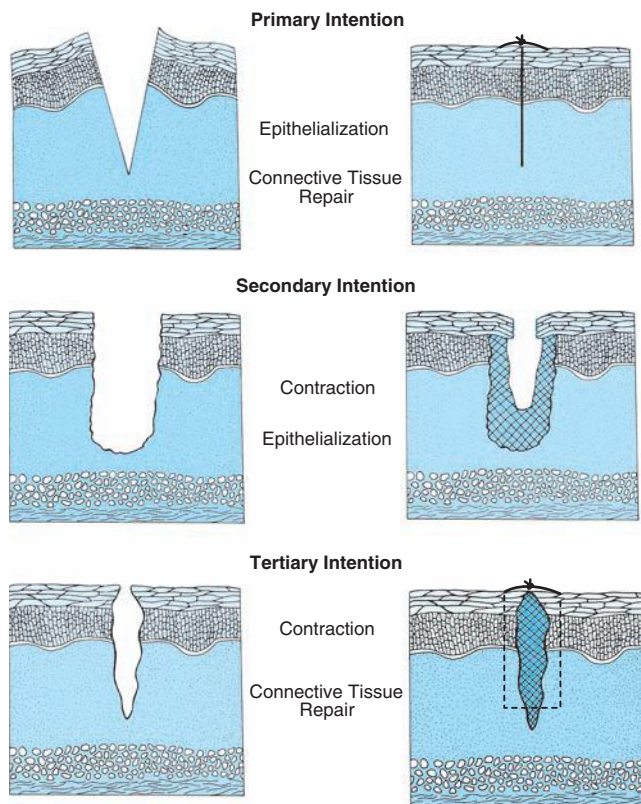


Figure 9-6. Different clinical approaches to the closure and healing of acute wounds.

Factors Affecting Wound Healing

Advanced Age. Most surgeons believe that aging produces intrinsic physiologic changes that result in delayed or impaired wound healing. Clinical experience with elderly patients tends to support this belief. Studies of hospitalized surgical patients show a direct correlation between older age and poor wound healing outcomes such as dehiscence and incisional hernia.^{57,58}

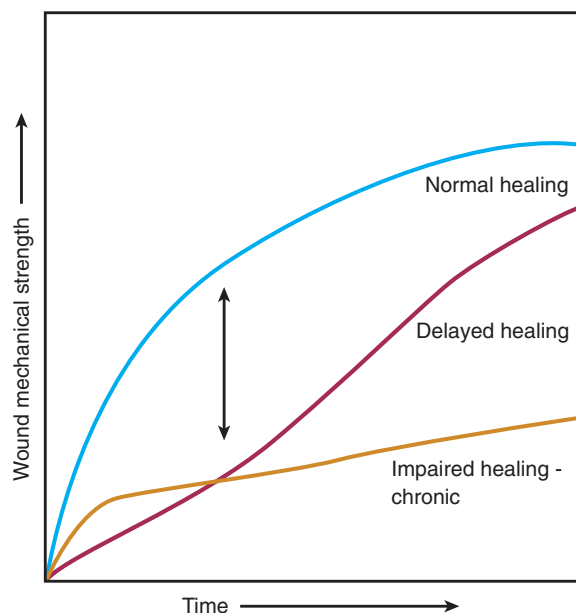


Figure 9-7. The acquisition of wound mechanical strength over time in normal, delayed, and impaired healing.

Table 9-6

Factors affecting wound healing*Systemic*

Age
Nutrition
Trauma
Metabolic diseases
Immunosuppression
Connective tissue disorders
Smoking

Local

Mechanical injury
Infection
Edema
Ischemia/necrotic tissue
Topical agents
Ionizing radiation
Low oxygen tension
Foreign bodies

However, these statistics fail to take into account underlying illnesses or diseases as a possible source of impaired wound healing in the elderly. The increased incidence of cardiovascular disease, metabolic diseases (diabetes mellitus, malnutrition, and vitamin deficiencies), and cancer, and the widespread use of drugs that impair wound healing may all contribute to the higher incidence of wound problems in the elderly. However, more recent clinical experience suggests that major operative interventions can be accomplished safely in the elderly.

The results of animal studies regarding the effects of aging on wound healing have yielded contradictory results. In healthy human volunteers, there was a significant delay of 1.9 days in the epithelialization of superficial skin defects in those older than 70 years of age when compared to younger volunteers.⁵⁹ In the same volunteers, using a micro-model of fibroplasia, no difference in DNA or hydroxyproline wound accumulation could be demonstrated between the young and elderly groups; however, the young volunteers had a significantly higher amount of total α -amino nitrogen in their wounds, a reflection of total protein content of the wound. Thus, although wound collagen synthesis does not seem to be impaired with advanced age, noncollagenous protein accumulation at wounded sites is decreased with aging, which may impair the mechanical properties of scarring in elderly patients.

Hypoxia, Anemia, and Hypoperfusion. Low oxygen tension has a profoundly deleterious effect on all aspects of wound healing. Fibroplasia, although stimulated initially by the hypoxic wound environment, is significantly impaired by local hypoxia. Optimal collagen synthesis requires oxygen as a cofactor, particularly for the hydroxylation steps. Increasing subcutaneous oxygen tension levels by increasing the fraction of inspired oxygen (F_{IO_2}) of inspired air for brief periods during and immediately following surgery results in enhanced collagen deposition and in decreased rates of wound infection after elective surgery.⁶⁰⁻⁶²

Major factors affecting local oxygen delivery include hypoperfusion either for systemic reasons (low volume or cardiac failure) or due to local causes (arterial insufficiency, local vasoconstriction, or excessive tension on tissues). The level of vasoconstriction of the subcutaneous capillary bed is exquisitely

responsive to fluid status, temperature, and hyperactive sympathetic tone as is often induced by postoperative pain. Correction of these factors can have a remarkable influence on wound outcome, particularly on decreasing wound infection rates.⁶¹⁻⁶³ Mild to moderate normovolemic anemia does not appear to adversely affect wound oxygen tension and collagen synthesis, unless the hematocrit falls below 15%.⁶³

Steroids and Chemotherapeutic Drugs. Large doses or chronic usage of glucocorticoids reduce collagen synthesis and wound strength.⁶⁴ The major effect of steroids is to inhibit the inflammatory phase of wound healing (angiogenesis, neutrophil and macrophage migration, and fibroblast proliferation) and the release of lysosomal enzymes. The stronger the anti-inflammatory effect of the steroid compound used, the greater the inhibitory effect on wound healing. Steroids used after the first 3 to 4 days postinjury do not affect wound healing as severely as when they are used in the immediate postoperative period. Therefore, if possible, their use should be delayed, or alternatively, forms with lesser anti-inflammatory effects should be administered.

In addition to their effect on collagen synthesis, steroids also inhibit epithelialization and contraction and contribute to increased rates of wound infection, regardless of the time of administration.⁶⁴ Steroid-delayed healing of cutaneous wounds can be stimulated to epithelialize by topical application of vitamin A.^{64,65} Collagen synthesis of steroid-treated wounds also can be stimulated by vitamin A.

All chemotherapeutic antimetabolite drugs adversely affect wound healing by inhibiting early cell proliferation and wound DNA and protein synthesis, all of which are critical to successful repair. Delay in the use of such drugs for about 2 weeks postinjury appears to lessen the wound healing impairment.⁶⁶ Extravasation of most chemotherapeutic agents is associated with tissue necrosis, marked ulceration, and protracted healing at the affected site.⁶⁷

Metabolic Disorders. Diabetes mellitus is the best known of the metabolic disorders contributing to increased rates of wound infection and failure.⁶⁸ Uncontrolled diabetes results in reduced inflammation, angiogenesis, and collagen synthesis. Additionally, the large- and small-vessel disease that is the hallmark of advanced diabetes contributes to local hypoxemia. Defects in granulocyte function, capillary ingrowth, and fibroblast proliferation all have been described in diabetes. Obesity, insulin resistance, hyperglycemia, and diabetic renal failure contribute significantly and independently to the impaired wound healing observed in diabetics.⁶⁹ In wound studies on experimental diabetic animals, insulin restores collagen synthesis and granulation tissue formation to normal levels if given during the early phases of healing.⁷⁰ In clean, noninfected, and well-perfused experimental wounds in human diabetic volunteers, type 1 diabetes mellitus was noted to decrease wound collagen accumulation in the wound, independent of the degree of glycemic control. Type 2 diabetic patients showed no effect on collagen accretion when compared to healthy, age-matched controls.⁷¹ Furthermore, the diabetic wound appears to be lacking in sufficient growth factor levels, which signal normal healing. It remains unclear whether decreased collagen synthesis or an increased breakdown due to an abnormally high proteolytic wound environment is responsible.

Careful preoperative correction of blood sugar levels improves the outcome of wounds in diabetic patients. Increasing the inspired oxygen tension, judicious use of antibiotics, and

correction of other coexisting metabolic abnormalities all can result in improved wound healing.

Uremia also has been associated with disordered wound healing. Experimentally, uremic animals demonstrate decreased wound collagen synthesis and breaking strength. The contribution of uremia alone to this impairment, rather than that of associated malnutrition, is difficult to assess.⁶⁹ The clinical use of dialysis to correct the metabolic abnormalities and nutritional restoration should impact greatly on the wound outcome of such patients.

Obesity is the largest growing public health problem in the United States and the world. Over 60% of Americans are overweight or obese. Uncomplicated obesity (i.e., in the absence of comorbid conditions such as cardiovascular disease, diabetes, or respiratory insufficiency) has by itself significant deleterious effects on wound healing. Visceral adiposity is active metabolically and immunologically and, through generation of proinflammatory cytokines and adipokines, leads to the development of the metabolic syndrome. Many of these molecules have effects on cells participating in the healing response. In nondiabetic obese rodents, wounds are mechanically weaker, and there is less dermal and reparative scar collagen. Pre-adipocytes infiltrate the dermis, and although they can evolve into fibroblasts, their regulatory mechanisms appear different from those of dermal or wound fibroblasts. Many studies indicate that obese patients have high rates of perioperative complications, with estimates as high as 30% for wound dehiscence, 17% for surgical site infections, 30% for incisional hernias, 19% for seromas, 13% for hematomas, and 10% for fat necrosis.^{72–74} Increased subcutaneous fat was associated with a 10-fold increased risk of surgery-related complications including anastomotic leaks, abdominal collection, and wound infections.⁷⁵ In many studies, obesity is a constant and major risk factor for hernia formation and recurrence after repair. The mechanism by which obesity impairs wound healing awaits complete delineation.

Nutrition. The importance of nutrition in the recovery from traumatic or surgical injury has been recognized by clinicians since the time of Hippocrates. Poor nutritional intake or lack of individual nutrients significantly alters many aspects of wound healing. The clinician must pay close attention to the nutritional status of patients with wounds, since wound failure or wound infections may be no more than a reflection of poor nutrition. Although the full interaction of nutrition and wound healing is still not fully understood, efforts are being made to develop wound-specific nutritional interventions and institute the pharmacologic use of individual nutrients as modulators of wound outcomes.

Experimental rodents fed either a 0% or 4% protein diet have impaired collagen deposition with a secondary decrease in skin and fascial wound-breaking strength and increased wound infection rates. Induction of energy-deficient states by providing only 50% of the normal caloric requirement leads to decreased granulation tissue formation and matrix protein deposition in rats. Acute fasting in rats markedly impairs collagen synthesis while decreasing procollagen mRNA.⁷⁶

Clinically, it is extremely rare to encounter pure energy or protein malnutrition, and the vast majority of patients exhibit combined protein-energy malnutrition. Such patients have diminished hydroxyproline accumulation (an index of collagen deposition) into subcutaneously implanted polytetrafluoroethylene tubes when compared to normally nourished patients (Fig. 9-8). Furthermore, malnutrition correlates clinically with enhanced rates of wound complications and increased wound failure

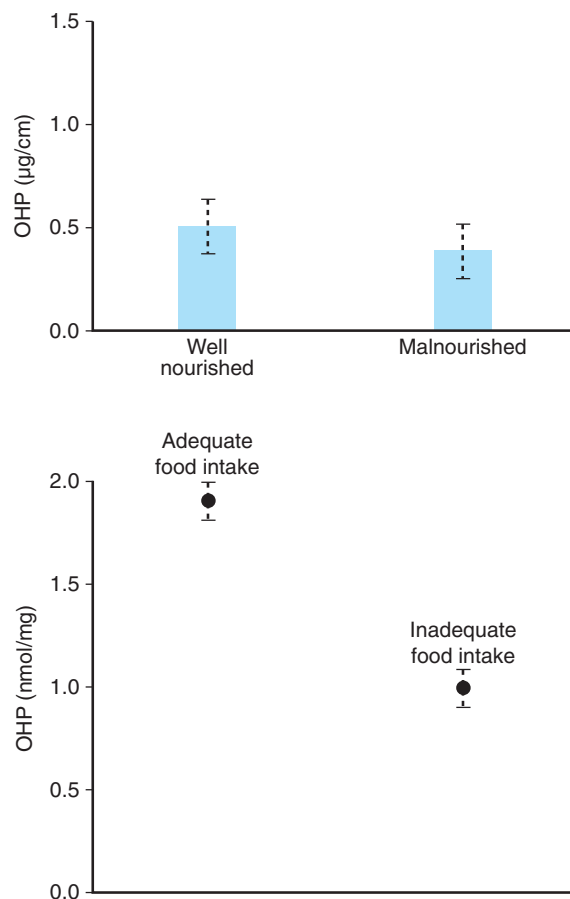


Figure 9-8. Effect of malnutrition on collagen deposition in experimental human wounds. OHP = hydroxyproline.

following diverse surgical procedures. This reflects impaired healing response as well as reduced cell-mediated immunity, phagocytosis, and intracellular killing of bacteria by macrophages and neutrophils during protein-calorie malnutrition.⁷⁶

Two additional nutrition-related factors warrant discussion. First, the degree of nutritional impairment need not be long-standing in humans, as opposed to the experimental situation. Thus patients with brief preoperative illnesses or reduced nutrient intake in the period immediately preceding the injury or operative intervention will demonstrate impaired fibroplasias.^{77,78} Second, brief and not necessarily intensive nutritional intervention, either via the parenteral or enteral route, can reverse or prevent the decreased collagen deposition noted with malnutrition or with postoperative starvation.⁷⁹

The possible role of single amino acids in enhanced wound healing has been studied for the last several decades. Arginine appears most active in terms of enhancing wound fibroplasia. Arginine deficiency results in decreased wound-breaking strength and wound-collagen accumulation in chow-fed rats. Rats that are given 1% arginine HCl supplementation, and therefore are not arginine-deficient, have enhanced wound-breaking strength and collagen synthesis when compared to chow-fed controls.⁸⁰ Studies have been carried out in healthy human volunteers to examine the effect of arginine supplementation on collagen accumulation. Young, healthy, human volunteers (aged 25–35 years) were found to have significantly increased wound-collagen deposition following oral supplementation with either 30 g of arginine aspartate (17 g of

free arginine) or 30 g of arginine HCl (24.8 g of free arginine) daily for 14 days.⁸¹ In a study of healthy older humans (aged 67–82 years), daily supplements of 30 g of arginine aspartate for 14 days resulted in significantly enhanced collagen and total protein deposition at the wound site when compared to controls given placebos. There was no enhanced DNA synthesis present in the wounds of the arginine-supplemented subjects, suggesting that the effect of arginine is not mediated by an inflammatory mode of action.⁸² In this and later studies, arginine supplementation, whether administered orally or parenterally, had no effect on the rate of epithelialization of a superficial skin defect. This further suggests that the main effect of arginine on wound healing is to enhance wound collagen deposition. Recently, a dietary supplemental regimen of arginine, β -hydroxy- β -methyl butyrate, and glutamine was found to significantly and specifically enhance collagen deposition in elderly, healthy human volunteers when compared to an isocaloric, isonitrogenous supplement (Fig. 9-9).⁸³ As increases in breaking strength during the first weeks of healing are directly related to new collagen synthesis, arginine supplementation may result in an improvement in wound strength as a consequence of enhanced collagen deposition.

The vitamins most closely involved with wound healing are vitamin C and vitamin A. Scurvy or vitamin C deficiency leads to a defect in wound healing, particularly via a failure in collagen synthesis and cross-linking. Biochemically, vitamin C is required for the conversion of proline and lysine to hydroxyproline and hydroxylysine, respectively. Vitamin C deficiency has also been associated with an increased incidence of wound infection, and if wound infection does occur, it tends to be more severe. These effects are believed to be due to an associated impairment in neutrophil function, decreased complement activity, and decreased walling-off of bacteria secondary to insufficient collagen deposition. The recommended dietary allowance is 60 mg daily. This provides a considerable safety margin for most

healthy nonsmokers. In severely injured or extensively burned patients, this requirement may increase to as high as 2 g daily. There is no evidence that excess vitamin C is toxic; however, there is no evidence that supertherapeutic doses of vitamin C are of any benefit.⁸⁴

Vitamin A deficiency impairs wound healing, while supplemental vitamin A benefits wound healing in nondeficient humans and animals. Vitamin A increases the inflammatory response in wound healing, probably by increasing the lability of lysosomal membranes. There is an increased influx of macrophages, with an increase in their activation and increased collagen synthesis. Vitamin A directly increases collagen production and epidermal growth factor receptors when it is added in vitro to cultured fibroblasts. As mentioned before, supplemental vitamin A can reverse the inhibitory effects of corticosteroids on wound healing. Vitamin A also can restore wound healing that has been impaired by diabetes, tumor formation, cyclophosphamide, and radiation. Serious injury or stress leads to increased vitamin A requirements. In the severely injured patient, supplemental doses of vitamin A have been recommended. Doses ranging from 25,000 to 100,000 IU per day have been advocated.

The connections between specific minerals and trace elements and deficits in wound healing are complex. Frequently, deficiencies are multiple and include macronutrient deficiencies. As with some of the vitamins described earlier, the specific trace element may function as a cofactor or part of an enzyme that is essential for homeostasis and wound healing. Clinically, preventing deficiencies is often easier to accomplish than diagnosing them.

Zinc is the most well-known element in wound healing and has been used empirically in dermatologic conditions for centuries. It is essential for wound healing in animals and humans. There are over 150 known enzymes for which zinc is either an integral part or an essential cofactor, and many of these enzymes are critical to wound healing.⁸⁵ With zinc deficiency, there is decreased fibroblast proliferation, decreased collagen synthesis, impaired overall wound strength, and delayed epithelialization. These defects are reversed by zinc supplementation. To date, no study has shown improved wound healing with zinc supplementation in patients who are not zinc deficient.⁸⁶

Infections. Wound infections continue to represent a major medical problem, both in terms of how they affect the outcome of surgical procedures (surgical site infections), and for their impact on the length of hospital stay and medical costs.⁸⁷ Many otherwise successful surgical operations fail because of the development of wound infections. The occurrence of infections is of major concern when implants are used, and their occurrence may lead to the removal of the prosthetic material, thus subjecting the patient to further operations and severe risk of morbidity and mortality. Infections can weaken an abdominal closure or hernia repair and result in wound dehiscence or recurrence of the hernia. Cosmetically, infections can lead to disfiguring, unsightly, or delayed closures.

Exhaustive studies have been undertaken that examine the appropriate prophylactic treatment of operative wounds. Bacterial contaminants normally present on skin are prevented from entry into deep tissues by intact epithelium. Surgery breaches the intact epithelium, allowing bacteria access to these tissues and the bloodstream. Antibiotic prophylaxis is most effective when adequate concentrations of antibiotic are present in the tissues at the time of incision, and assurance of adequate preoperative antibiotic dosing and timing has become a significant

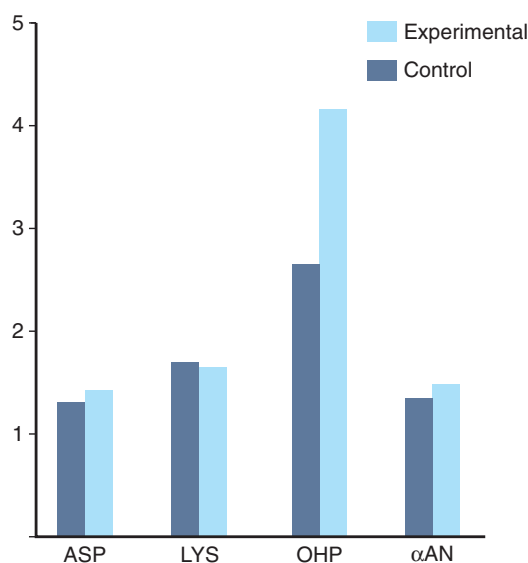


Figure 9-9. Ratios of 14-day to 7-day values for aspartate (ASP), hydroxyproline (OHP), lysine (LYS), and α -amino nitrogen (α AN) in volunteers given dietary supplements of arginine, β -hydroxy- β -methylbutyrate, and glutamine. * $P < .05$. (Reproduced with permission from Williams JZ, Abumrad NN, Barbul A. Effect of a specialized amino acid mixture on human collagen deposition. *Ann Surg*. 2002;236:369.)

hospital performance measure.⁸⁸ Addition of antibiotics after operative contamination has occurred clearly is ineffective in preventing postoperative wound infections.

Studies that compare operations performed with and without antibiotic prophylaxis demonstrate that class II, III, and IV procedures (see below) treated with appropriate prophylactic antibiotics have only one third the wound infection rate of previously reported untreated series.⁸⁹ More recently, repeat dosing of antibiotics has been shown to be essential in decreasing postoperative wound infections in operations with durations exceeding the biochemical half-life ($t_{1/2}$) of the antibiotic or in which there is large-volume blood loss and fluid replacement.^{90,91} In lengthy cases, those in which prosthetic implants are used, or when unexpected contamination is encountered, additional doses of antibiotic may be administered for 24 hours postoperatively.

Selection of antibiotics for use in prophylaxis should be tailored to the type of surgery to be performed, operative contaminants that might be encountered during the procedure, and the profile of resistant organisms present at the institution where the surgery is performed. The continuing widespread appearance of methicillin-resistant *Staphylococcus aureus* (MRSA), and vancomycin-resistant enterococci (VRE) has significantly restricted the selection of these agents for routine use. Surgery-specific treatment guidelines are provided in Table 9-7.⁹⁰

Patients with prosthetic heart valves or any implanted vascular or orthopedic prostheses should receive antibiotic prophylaxis prior to any procedure in which significant bacteremia is anticipated. Dental procedures require prophylaxis with broad-spectrum penicillins or amoxicillin, while urologic instrumentation should be pretreated with a second-generation cephalosporin. Patients with prostheses who undergo gastrointestinal surgery should receive anaerobic coverage combined with a cephalosporin. Nasal screening and decolonization for *Staphylococcus aureus* carriers is recommended for selected procedures (i.e., cardiac, orthopedic, neurosurgical procedures with implants).

The incidence of wound infection is about 5% to 10% nationwide and has not changed during the last few decades. Quantitatively, it has been shown that if the wound is contaminated with $>10^5$ microorganisms, the risk of wound infection is markedly increased, but this threshold may be much lower in the presence of foreign materials. The source of pathogens for the infection is usually the endogenous flora of the patient's skin, mucous membranes, or from hollow organs. The most common organisms responsible for wound infections in order of frequency are *Staphylococcus* species, coagulase-negative *Streptococcus*, enterococci, and *Escherichia coli*. The incidence of wound infection bears a direct relationship to the degree of contamination that occurs during the operation from the disease process itself (clean—class I, clean contaminated—class II, contaminated—class III, and dirty—class IV). Many factors contribute to the development of postoperative wound infections. Most surgical wound infections become apparent within 7 to 10 days postoperatively, although a small number manifest years after the original operative intervention. With the hospital stay becoming shorter and shorter, many infections are detected in the outpatient setting, leading to underreporting of the true incidence of wound infections absent intensive surveillance. There has been much debate about the actual definition of wound infection. The narrowest definition would include wounds that drain purulent material with bacteria identified on culture. The more broad definition would include all wounds

draining pus, whether or not the bacteriologic studies are positive; wounds that are opened by the surgeon; and wounds that the surgeon considers infected.⁹²

Anatomically, wound infections can be classified as superficial incisional, deep incisional, and organ/space wound infections, involving fascia, muscle, or the abdominal cavity. About three fourths of all wound infections are superficial, involving skin and subcutaneous tissue only. Clinical diagnosis is easy when a postoperative wound looks edematous and erythematous and is tender. Often the presentation is more subtle, and development of postoperative fever, usually low-grade; development of a mild and unexplained leukocytosis; or the presence of undue incisional pain should direct attention to the wound. Inspection of the wound is most useful in detecting subtle edema around the suture or staple line, manifested as a waxy appearance of the skin, which characterizes the early phase of infection. If a wound infection is suspected, several stitches or staples around the most suspicious area should be removed with insertion of a cotton-tipped applicator into the subcutaneous area to open a small segment of the incision. This causes minimal if any discomfort to the patient. Presence of pus mandates further opening of the subcutaneous and skin layers to the full extent of the infected pocket. Samples should be taken for aerobic and anaerobic cultures, with very few patients requiring antibiotic therapy. Patients who are immunosuppressed (diabetics and those on steroids or chemotherapeutic agents), who have evidence of tissue penetration or systemic toxicity, or who have had prosthetic devices inserted (vascular grafts, heart valves, artificial joints, or mesh) should be treated with systemic antibiotics.⁹²

Deep wound infections arise immediately adjacent to the fascia, either above or below it, and often have an intra-abdominal component. Most intra-abdominal infections do not, however, communicate with the wound. Deep infections present with fever and leukocytosis. The incision may drain pus spontaneously, or the intra-abdominal extension may be recognized following the drainage of what was thought to be a superficial wound infection, but pus draining between the fascial sutures will be noted. Sometimes wound dehiscence will occur.

The most dangerous of the deep infections is necrotizing fasciitis. It results in high mortality, particularly in the elderly. This is an invasive process that involves the fascia and leads to secondary skin necrosis. Pathophysiologically, it is a septic thrombosis of the vessels between the skin and the deep layers. The skin demonstrates hemorrhagic bullae and subsequent frank necrosis, with surrounding areas of inflammation and edema. The fascial necrosis is usually wider than the skin involvement or than the surgeon estimates on clinical grounds. The patient is toxic and has high fever, tachycardia, and marked hypovolemia, which if uncorrected, progresses to cardiovascular collapse. Bacteriologically, this is a mixed infection, and samples should be obtained for Gram stain smears and cultures to aid in diagnosis and treatment. As soon as bacteriologic studies have been obtained, high-dose penicillin treatment needs to be started (20–40 million U/d intravenously) due to concern over the presence of *Clostridia perfringens* and other related species; broad-spectrum antibiotics should be added and the regimen modified based on culture results. Cardiovascular resuscitation with electrolyte solutions, blood, and/or plasma is carried out as expeditiously as possible prior to induction of anesthesia. The aim of surgical treatment is thorough removal of all necrosed skin and fascia. If viable skin overlies necrotic fascia, multiple longitudinal skin incisions can be made to allow for excision of the devitalized fascia.

Table 9-7

Antimicrobial prophylaxis for surgery

NATURE OF OPERATION	COMMON PATHOGENS	RECOMMENDED ANTIMICROBIALS	ADULT DOSAGE BEFORE SURGERY ¹
Cardiac	<i>Staphylococcus aureus</i> , <i>S. epidermidis</i>	Cefazolin <i>or</i> Cefuroxime <i>or</i> Vancomycin ⁴	1–2 g IV ^{2,3} 1.5 g IV ³ 1 g IV
Gastrointestinal			
esophageal/gastroduodenal	Enteric gram-negative bacilli, gram-positive cocci	High risk ⁵ only: cefazolin ⁶	1–2 g IV ²
Biliary tract	Enteric gram-negative bacilli, enterococci, clostridia	High risk ⁷ only: cefazolin ^{6,8}	1–2 g IV ²
Colorectal	Enteric gram-negative bacilli, anaerobes, enterococci	Oral: neomycin + erythromycin base ⁹ <i>or</i> metronidazole ⁹ Parenteral: cefoxitin ⁶ <i>or</i> Cefotetan ⁶ <i>or</i> Cefazolin + Metronidazole ⁶ <i>or</i> Ampicillin/sulbactam	—see note 9 1–2 g IV 1–2 g IV 1–2 g IV ² 0.5 g IV 3 g IV
Appendectomy, nonperforated ¹¹	Same as for colorectal	Cefoxitin ⁶ <i>or</i> cefotetan ⁶ <i>or</i> Cefazolin ⁶ + Metronidazole	1–2 g IV 1–2 g IV ² 0.5 g IV
Genitourinary			
Cystoscopy alone	Enteric gram-negative bacilli, enterococci	High risk only ¹² : ciprofloxacin ¹⁰ <i>or</i> Trimethoprim-sulfamethoxazole	500 mg PO <i>or</i> 400 mg IV 1 DS tablet
Cystoscopy with manipulation <i>or</i> upper tract instrumentation ¹³	Enteric gram-negative bacilli, enterococci	Ciprofloxacin ¹⁰ <i>or</i> Trimethoprim-sulfamethoxazole	500 mg PO <i>or</i> 400 mg IV 1 DS tablet
Open <i>or</i> laparoscopic surgery ¹⁴	Enteric gram-negative bacilli, enterococci	Cefazolin ⁶	1–2 g IV ²
Gynecologic and obstetric			
Vaginal, abdominal, <i>or</i> laparoscopic hysterectomy	Enteric gram-negative bacilli, anaerobes, group B streptococci, enterococci	Cefazolin ⁶ <i>or</i> cefoxitin ⁶ <i>or</i> cefotetan ⁶ <i>or</i> Ampicillin/sulbactam ^{6,10}	1–2 g IV ² 3 g IV
Cesarean section	Same as for hysterectomy	Cefazolin ⁶	1–2 g IV ²
Abortion, surgical	Same as for hysterectomy	Doxycycline	300 mg PO ¹⁵
Head and neck surgery			
Incisions through oral <i>or</i> pharyngeal mucosa	Anaerobes, enteric gram-negative bacilli, <i>S. aureus</i>	Clindamycin <i>or</i> Cefazolin + Metronidazole <i>or</i> Ampicillin/sulbactam ¹⁰	600–900 mg IV 1–2 g IV ² 0.5 g IV 3 g IV
Neurosurgery	<i>S. aureus</i> , <i>S. epidermidis</i>	Cefazolin	1–2 g IV ²
Ophthalmic	<i>S. epidermidis</i> , <i>S. aureus</i> , streptococci, enteric gram-negative bacilli, <i>Pseudomonas</i> spp.	Gentamicin, tobramycin, ciprofloxacin, gatifloxacin, levofloxacin, moxifloxacin, ofloxacin <i>or</i> neomycin-gramicidin-polymyxin B <i>OR</i> cefazolin	Multiple drops topically over 2 to 24 hours 100 mg subconjunctivally
Orthopedic	<i>S. aureus</i> , <i>S. epidermidis</i>	Cefazolin ¹⁶ <i>or</i> Vancomycin ^{2,16}	1–2 g IV ² , 1 g IV
Thoracic (noncardiac)	<i>S. aureus</i> , <i>S. epidermidis</i> , streptococci, enteric gram-negative bacilli	Cefazolin <i>or</i> Ampicillin/sulbactam ¹⁰ <i>or</i> Vancomycin ⁴	1–2 g IV ² 3 g IV 1 g IV

Table 9-7

Antimicrobial prophylaxis for surgery

NATURE OF OPERATION	COMMON PATHOGENS	RECOMMENDED ANTIMICROBIALS	ADULT DOSAGE BEFORE SURGERY ¹
Vascular Arterial surgery involving a prosthesis, the abdominal aorta, or a groin incision	<i>S. aureus</i> , <i>S. epidermidis</i> , enteric gram-negative bacilli	Cefazolin <i>or</i> Vancomycin ⁴	1–2 g IV ² 1 g IV
Lower extremity amputation for ischemia	<i>S. aureus</i> , <i>S. epidermidis</i> , enteric gram-negative bacilli, clostridia	Cefazolin <i>or</i> Vancomycin ⁴	1–2 g IV ² 1 g IV

¹Parenteral prophylactic antimicrobials can be given as a single IV dose begun within 60 min before the operation. For prolonged operations (>3 h) or those with major blood loss, or in patients with extensive burns, additional intraoperative doses should be given at intervals 1–2 times the half-life of the drug (ampicillin/sulbactam q2 h, cefazolin q4 h, cefuroxime q4 h, cefoxitin q2 h, clindamycin q6 h, vancomycin q12 h) for the duration of the procedure in a patient with normal renal function. If vancomycin or a fluoroquinolone is used, the infusion should be started 60–120 min before the initial incision to minimize the possibility of an infusion reaction close to the time of induction of anesthesia and to have adequate tissue levels at the time of incision.

²The recommended dose of cefazolin is 1 g for patients who weigh 80 kg and 2 g for those >80 kg. Morbidly obese patients may need higher doses.

³Some experts recommend an additional dose when patients are removed from bypass during open heart surgery.

⁴Vancomycin can be used in hospitals in which methicillin-resistant *Staphylococcus aureus* (MRSA) and *S. epidermidis* are a frequent cause of postoperative wound infection, in patients previously colonized with MRSA, or for those who are allergic to penicillin or cephalosporins. Rapid IV administration may cause hypotension, which could be especially dangerous during induction of anesthesia. Even when the drug is given over 60 min, hypotension may occur; treatment with diphenhydramine (Benadryl and others) and further slowing of the infusion rate may be helpful. Some experts would give 15 mg/kg of vancomycin to patients weighing more than 75 kg up to a maximum of 1.5 g with a slower infusion rate (90 min for 1.5 g). For procedures in which gram-negative bacilli are common pathogens, many experts would add another drug such as an aminoglycoside (gentamicin, tobramycin, or amikacin), aztreonam, or a fluoroquinolone.

⁵Morbid obesity, GI obstruction, decreased gastric acidity or gastrointestinal motility, gastric bleeding, malignancy or perforation, or immunosuppression.

⁶For patients allergic to penicillin and cephalosporins, clindamycin or vancomycin with either gentamicin, ciprofloxacin, levofloxacin, or aztreonam is a reasonable alternative. Fluoroquinolones should not be used for prophylaxis in cesarean section.

⁷Age >70 y, acute cholecystitis, nonfunctioning gallbladder, obstructive jaundice, or common duct stones.

⁸Cefotetan, cefoxitin, and ampicillin/sulbactam are reasonable alternatives.

⁹In addition to mechanical bowel preparation, 1 g of neomycin plus 1 g of erythromycin at 1 P.M., 2 P.M., and 11 P.M. or 2 g of neomycin plus 2 g of metronidazole at 7 P.M. and 11 P.M. the day before an 8 A.M. operation.

¹⁰Due to increasing resistance of *E. coli* to fluoroquinolones and ampicillin/sulbactam, local sensitivity profiles should be reviewed prior to use.

¹¹For a ruptured viscus, therapy is often continued for about 5 d.

¹²Urine culture positive or unavailable, preoperative catheter, transrectal prostate biopsy, or placement of prosthetic material.

¹³Shock wave lithotripsy, ureteroscopy.

¹⁴Including percutaneous renal surgery, procedures with entry into the urinary tract, and those involving implantation of a prosthesis. If manipulation of bowel is involved, prophylaxis is given according to colorectal guidelines.

¹⁵Divided into 100 mg before procedure and 200 mg after.

¹⁶If a tourniquet is to be used in the procedure, the entire dose of antibiotic must be infused prior to its inflation.

Source: Reprinted with special permission from *Treatment Guidelines from The Medical Letter*, October 2012; Vol. 10(122):73. www.medicalletter.org.

Although removal of all necrotic tissue is the goal of the first surgical intervention, the distinction between necrotic and simply edematous tissue often is difficult. Careful inspection every 12 to 24 hours will reveal any new necrotic areas, and these need further débridement and excision. When all necrotic tissue has been removed and the infection has been controlled, the wounds may be covered with homo- or xenografts until definitive reconstruction and autografting can take place.

The mere presence of bacteria in an open wound, either acute or chronic, does not constitute an infection, because large numbers of bacteria can be present in the normal situation. In addition, the bacteria identified by cultures may not be representative of the bacteria causing the actual wound infection. There seems to be confusion as to what exactly constitutes wound infection. For purposes of clarity, we have to differentiate between contamination, colonization, and infection. *Contamination* is the presence of bacteria without multiplication, *colonization* is multiplication without host response, and *infection* is the presence of host response in reaction to deposition and multiplication of bacteria. The presence of a host response helps to differentiate between infection and colonization as seen in chronic wounds. The host response that helps in diagnosing wound infection comprises cellulitis, abnormal

discharge, delayed healing, change in pain, abnormal granulation tissue, bridging, and abnormal color and odor.

As discussed previously, neutrophils play a major role in preventing wound infections. Chronic granulomatous disease (CGD) comprises a genetically heterogeneous group of diseases in which the reduced nicotinamide adenine dinucleotide phosphate (NADPH)-dependent oxidase enzyme is deficient. This defect impairs the intracellular killing of microorganisms, leaving the patient liable to infection by bacteria and fungi. Afflicted patients have recurrent infections and form granulomas, which can lead to obstruction of the gastric antrum and genitourinary tracts and poor wound healing. Surgeons become involved when the patient develops infectious or obstructive complications.

The nitroblue tetrazolium (NBT) reduction test is used to diagnose CGD. Normal neutrophils can reduce this compound, while neutrophils from affected patients do not, facilitating the diagnosis via a colorimetric test. Clinically, patients develop recurrent infections such as pneumonia, lymphadenitis, hepatic abscess, and osteomyelitis. Organisms most commonly responsible are *Staphylococcus aureus*, *Aspergillus*, *Klebsiella*, *Serratia*, or *Candida*. When CGD patients require surgery, a preoperative pulmonary function test should be considered since they are

predisposed to obstructive and restrictive lung disease. Wound complications, mainly infection, are common. Sutures should be removed as late as possible since the wounds heal slowly. Abscess drains should be left in place for a prolonged period until the infection is completely resolved.⁹³

Hyperglycemia has been shown to be a significant risk factor of postoperative infections.⁹⁴ Tight blood glucose control, beginning preoperatively and continued into the operating room and beyond, has been associated with significant reduction in infectious complications, in particular following cardiac surgery.^{95,96} Too tight of a glycemic control (80–100 mg/dL) appears to be associated with more complications and is as effective, if not less than, moderate control (120–180 mg/dL).^{97,98}

Another host factor that has been implicated in the development of superficial surgical site infection relates to the state of the subcutaneous capillary bed. Thomas K. Hunt had shown through several decades of work that this capillary bed is exquisitely sensitive to hypovolemia,⁹⁹ hypothermia,¹⁰⁰ and stress, leading to rapid vasoconstriction with secondary impaired oxygen delivery and increased rates of infection.⁶¹ Maintenance of euvolemia, core temperature above 36 to 36.5°C, and pain control have all been shown singly and additively to reduce rates of wound infections.⁶³ Another suggestion has been to increase inspired FiO_2 to 0.8 for the duration of the operation and in the immediate postoperative period, as a means of increasing subcutaneous tissue oxygen delivery. Although successful in most studies,^{62,101} there have also been negative results from such a single approach¹⁰²; this suggests that addressing volume, temperature, pain control, and oxygen delivery in concert may be the more fruitful approach to reduce surgical wound infections.

Chronic Wounds

Chronic wounds are defined as wounds that have failed to proceed through the orderly process that produces satisfactory anatomic and functional integrity or that have proceeded through the repair process without producing an adequate anatomic and functional result. The majority of wounds that have not healed in 3 months are considered chronic. *Skin ulcers*, which usually occur in traumatized or vascular compromised soft tissue, are also considered chronic in nature, and proportionately are the major component of chronic wounds. In addition to the factors discussed earlier that can delay wound healing, other causative mechanisms may also play a role in the etiology of chronic wounds. Repeated trauma, poor perfusion or oxygenation, and/or excessive inflammation contribute to the causation and the perpetuation of the chronicity of wounds.

Unresponsiveness to normal regulatory signals also has been implicated as a predictive factor of chronic wounds. This may come about as a failure of normal growth factor synthesis,¹⁰³ and thus an increased breakdown of growth factors within a wound environment that is markedly proteolytic because of overexpression of protease activity or a failure of the normal antiprotease inhibitor mechanisms.¹⁰⁴ Fibroblasts from chronic wounds also have been found to have decreased proliferative potential, perhaps because of senescence¹⁰⁵ or decreased expression of growth factor receptors.¹⁰⁶ Chronic wounds occur due to various etiologic factors, and several of the most common are discussed later.

Malignant transformation of chronic ulcers can occur in any long-standing wound (Marjolin's ulcer). Any wound that does not heal for a prolonged period of time is prone to malignant transformation. Malignant wounds are differentiated clinically from nonmalignant wounds by the presence of overturned

wound edges (Fig. 9-10). In patients with suspected malignant transformations, biopsy of the wound edges must be performed to rule out malignancy. Cancers arising *de novo* in chronic wounds include both squamous and basal cell carcinomas.

Ischemic Arterial Ulcers. These wounds occur due to a lack of blood supply and are painful at presentation. They usually are associated with other symptoms of peripheral vascular disease, such as intermittent claudication, rest pain, night pain, and color or trophic changes. These wounds commonly are present at the most distal portions of the extremities such as the interdigital clefts, although more proximal locations are also encountered. On examination, there may be diminished or absent pulses with decreased ankle-brachial index and poor formation of granulation tissue. Other signs of peripheral ischemia, such as dryness of skin, hair loss, scaling, and pallor can be present. The wound itself usually is shallow with smooth margins, and a pale base and surrounding skin may be present. The management of these wounds is two-pronged and includes revascularization and wound care.¹⁰⁷ Nonhealing of these wounds is the norm unless successful revascularization is performed. After establishing adequate blood supply, most such wounds progress to heal satisfactorily.

A strategy of prevention is extremely important in the approach to patients with limb ischemia. In bedridden patients, especially those who are sedated (in the intensive care unit), demented, or with peripheral neural compromise (neuropathy or paraplegia), pressure ulcers develop rapidly and often unnecessarily. Removal of restrictive stockings (in patients with critical ischemia), frequent repositioning, and surveillance are vital to preventing these ulcers.¹⁰⁸

Venous Stasis Ulcers. Although there is unanimous agreement that venous ulcers are due to venous stasis and hydrostatic back pressure, there is less consensus as to what are the exact pathophysiologic pathways that lead to ulceration and impaired healing. On the microvascular level, there is alteration and distention of the dermal capillaries with leakage of fibrinogen into the tissues; polymerization of fibrinogen into fibrin cuffs leads to perivascular cuffing that can impede oxygen exchange, thus contributing to ulceration. These same fibrin cuffs and the leakage of macromolecules such as fibrinogen and α_2 -macroglobulin trap growth factors and impede wound healing.¹⁰³ Another hypothesis suggests that neutrophils adhere to the capillary endothelium and cause plugging with diminished dermal blood flow. Venous hypertension and capillary damage lead to extravasation of hemoglobin. The products of this breakdown are irritating and cause pruritus and skin damage. The resulting brownish pigmentation of skin combined with the loss of subcutaneous fat produces characteristic changes called lipodermatosclerosis. Regardless of the pathophysiologic mechanisms, the clinically characteristic picture is that of an ulcer that fails to re-epithelialize despite the presence of adequate granulation tissue.

Venous stasis occurs due to the incompetence of either the superficial or deep venous systems. Chronic venous ulcers usually are due to the incompetence of the deep venous system and are commonly painless. Stasis ulcers tend to occur at the sites of incompetent perforators, the most common being above the medial malleolus, over Cockett's perforator. Upon examination, the typical location combined with a history of venous incompetence and other skin changes is diagnostic. The wound usually is shallow with irregular margins and pigmented surrounding skin.

The cornerstone of treatment of venous ulcers is compression therapy, although the best method to achieve it remains



Figure 9-10. Typical appearance of the malignant transformation of a long-standing chronic wound. (Photos used with permission by Dr. Robert S. Kirsner, University of Miami.)

controversial. Compression can be accomplished via rigid or flexible means. The most commonly used method is the rigid, zinc oxide-impregnated, nonelastic bandage. Others have proposed a four-layered bandage approach as a more optimal method of obtaining graduated compression.¹⁰⁹ Wound care in these patients focuses on maintaining a moist wound environment, which can be achieved with hydrocolloids. Other, more modern approaches include use of vasoactive substances and growth factor application, as well as the use of skin substitutes. Recently, sprayed allogeneic keratinocytes and fibroblasts plus four-layer bandages have been shown to hasten healing when compared to compression alone.¹¹⁰ Most venous ulcers can be healed with perseverance and by addressing the venous hypertension.¹⁰⁹ Unfortunately, recurrences are frequent despite preventative measures, largely because of patients' lack of compliance.¹¹¹

Diabetic Wounds. Ten percent to 25% of diabetic patients run the risk of developing ulcers. There are approximately 50,000 to 60,000 amputations performed in diabetic patients each year in the United States. The major contributors to the formation of diabetic ulcers include neuropathy, foot deformity, and ischemia. It is estimated that 60% to 70% of diabetic ulcers are due to neuropathy, 15% to 20% are due to ischemia, and another 15% to 20% are due to a combination of both. The neuropathy is both sensory and motor and is secondary to persistently elevated glucose levels. The loss of sensory function allows unrecognized injury to occur from ill-fitting shoes, foreign bodies, or other trauma. The motor neuropathy or Charcot's foot leads to collapse or dislocation of the interphalangeal or metatarsophalangeal joints, causing pressure on

areas with little protection. There is also severe micro- and macrovascular circulatory impairment.

Once ulceration occurs, the chances of healing are poor. The treatment of diabetic wounds involves local and systemic measures.¹¹² Achievement of adequate blood sugar levels is very important. Most diabetic wounds are infected, and eradication of the infectious source is paramount to the success of healing. Treatment should address the possible presence of osteomyelitis and should employ antibiotics that achieve adequate levels both in soft tissue and bone. Wide débridement of all necrotic or infected tissue is another cornerstone of treatment. Off-loading of the ulcerated area by using specialized orthotic shoes or casts allows for ambulation while protecting the fragile wound environment. Topical application of PDGF and granulocyte-macrophage colony-stimulating factor has met with limited but significant success in achieving closure.¹¹³ The application of engineered skin allograft substitutes, although expensive, also has shown some significant success.¹¹⁴ Prevention and specifically foot care play an important role in the management of diabetics.¹¹⁵

Decubitus or Pressure Ulcers. The incidence of pressure ulcers ranges from 2.7% to 9% in the acute care setting, in comparison to 2.4% to 23% in long-term care facilities. A pressure ulcer is a localized area of tissue necrosis that develops when soft tissue is compressed between a bony prominence and an external surface. Excessive pressure causes capillary collapse and impedes the delivery of nutrients to body tissues. Pressure ulcer formation is accelerated in the presence of friction, shear forces, and moisture. Other contributory factors in the pathogenesis of pressure ulcers include immobility, altered activity

levels, altered mental status, chronic conditions, and altered nutritional status. The four stages of pressure ulcer formation are as follows: stage I, nonblanching erythema of intact skin; stage II, partial-thickness skin loss involving epidermis or dermis or both; stage III, full-thickness skin loss, but not through the fascia; and stage IV, full-thickness skin loss with extensive involvement of muscle and bone.

The treatment of established pressure ulcers is most successful when carried out in a multidisciplinary manner by involving wound care teams consisting of physicians, nurses, dietitians, physical therapists, and nutritionists. Care of the ulcer itself comprises débridement of all necrotic tissue, maintenance of a favorable moist wound environment that will facilitate healing, relief of pressure, and addressing host issues such as nutritional, metabolic, and circulatory status. Débridement is most efficiently carried out surgically, but enzymatic proteolytic preparations and hydrotherapy also are used. The wound bed should be kept moist by employing dressings that absorb secretions but do not desiccate the wound.¹¹⁶ Operative repair, usually involving flap rotation, has been found to be useful in obtaining closure. Unfortunately, recurrence rates are extremely high, owing to the population at risk and the inability to fully address the causative mechanisms.¹¹⁷

EXCESS HEALING

Clinically, excess healing can be as significant as wound failure. It is likely that more operative interventions are required for correction of the morbidity associated with excessive healing than are required for wound failure. The clinical manifestations of exuberant healing are protean and differ in the skin (mutilating or debilitating scars, burn contractions), tendons (frozen repairs), the GI tract (strictures or stenoses), solid organs (cirrhosis, pulmonary fibrosis), or the peritoneal cavity (adhesive disease).

Hypertrophic scars (HTSs) and keloids represent an overabundance of fibroplasia in the dermal healing process. HTSs rise above the skin level but stay within the confines of the original wound and often regress over time. Keloids rise above the skin level as well, but extend beyond the border of the original wound and rarely regress spontaneously (Fig. 9-11). Both HTSs and keloids occur after trauma to the skin and may be tender, pruritic, and cause a burning sensation. Keloids are 15 times more common in darker-pigmented ethnicities, with individuals of African, Spanish, and Asian ethnicities being especially susceptible. Men and women are equally affected. Genetically, the predilection to keloid formation appears to be autosomal dominant with incomplete penetration and variable expression.^{117,118}

HTSs usually develop within 4 weeks after trauma. The risk of HTS increases if epithelialization takes longer than 21 days, independent of site, age, and race. Rarely elevated more than 4 mm above the skin level, HTSs stay within the boundaries of the wound. They usually occur across areas of tension and flexor surfaces, which tend to be at right angles to joints or skin creases. The lesions are initially erythematous and raised and over time may evolve into pale, flatter scars.

Keloids can result from surgery, burns, skin inflammation, acne, chickenpox, zoster, folliculitis, lacerations, abrasions, tattoos, vaccinations, injections, insect bites, or ear piercing, or may arise spontaneously. Keloids tend to occur 3 months to years after the initial insult, and even minor injuries can result in large lesions. They vary in size from a few millimeters to large,

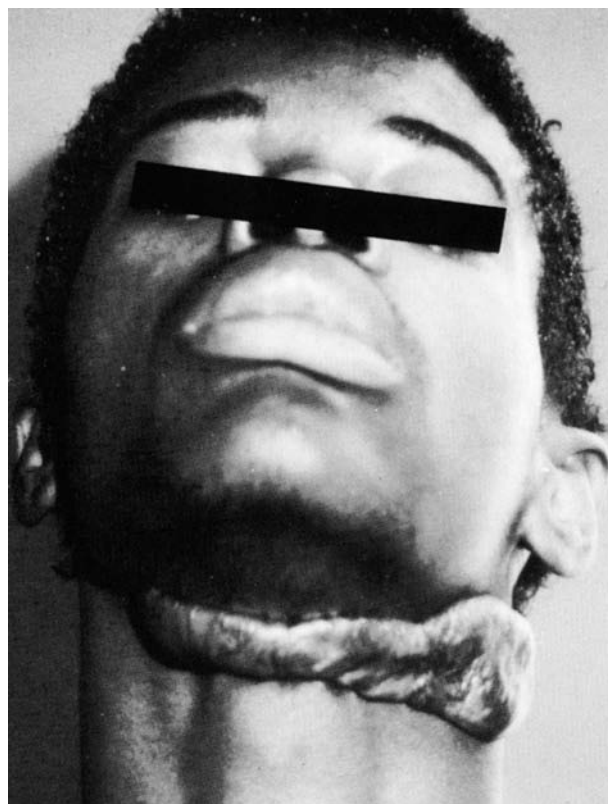


Figure 9-11. Recurrent keloid on the neck of a 17-year-old patient that had been revised several times. (Reproduced with permission from Murray JC, Pinnell SR. *Keloids and excessive dermal scarring*. In: Cohen IK, Diegelmann RF, Lindblad WJ, eds. *Wound Healing: Biochemical and Clinical Aspects*. Philadelphia: WB Saunders; 1993. Copyright Elsevier.)

pedunculated lesions with a soft to rubbery or hard consistency. While they project above surrounding skin, they rarely extend into underlying subcutaneous tissues. Certain body sites have a higher incidence of keloid formation, including the skin of the earlobe as well as the deltoid, presternal, and upper back regions. They rarely occur on eyelids, genitalia, palms, soles, or across joints. Keloids rarely involute spontaneously, and surgical intervention can lead to recurrence, often with a worse result (Table 9-8).

Histologically, both HTSs and keloids demonstrate increased thickness of the epidermis with an absence of rete ridges. There is an abundance of collagen and glycoprotein deposition. Normal skin has distinct collagen bundles, mostly parallel to the epithelial surface, with random connections between bundles by fine fibrillar strands of collagen. In HTS, the collagen bundles are flatter and more random, and the fibers are in a wavy pattern. In keloids, the collagen bundles are virtually nonexistent, and the fibers are connected haphazardly in loose sheets with a random orientation to the epithelium. The collagen fibers are larger and thicker, and myofibroblasts are generally absent.¹¹⁹

Keloidal fibroblasts have normal proliferation parameters but synthesize collagen at a rate 20 times greater than that observed in normal dermal fibroblasts, and 3 times higher than fibroblasts derived from HTS. Abnormal amounts of extracellular matrix such as fibronectin, elastin, and proteoglycans also are produced. The synthesis of fibronectin, which promotes clot generation, granulation tissue formation, and re-epithelialization,

TABLE 9-8

Characteristics of keloids and hypertrophic scars

	KELOID	HYPERTROPHIC SCAR
Incidence	Rare	Frequent
Ethnic groups	African American, Asian, Hispanic	No predilection
Prior injury	Yes	Yes
Site predilection	Neck, chest, ear lobes, shoulders, upper back	Anywhere
Genetics	Autosomal dominant with incomplete penetration	No
Timing	Symptom-free interval; may appear years after injury	4–6 weeks postinjury
Symptoms	Pain, pruritus, hyperesthesia, growth beyond wound margins	Raised, some pruritus, respects wound confines
Regression	No	Frequent spontaneous
Contracture	Rare	Frequent
Histology	Hypocellular, thick, wavy collagen fibers in random orientation	Parallel orientation of collagen fibers

decreases during the normal healing process; however, production continues at high levels for months to years in HTSs and keloids. This perturbed synthetic activity is mediated by altered growth factor expression. TGF- β expression is higher in HTS, and both HTS- and keloid-derived fibroblasts respond to lower concentrations of TGF- β than do normal dermal fibroblasts. HTSs also express increased levels of insulin-like growth factor-1, which reduces collagenase mRNA activity and increases mRNA for types I and II procollagen.¹²⁰ Keloid fibroblasts have enhanced expression of TGF- β 1 and TGF- β 2, VEGF, and plasminogen activator inhibitor-1 and an increased number of PDGF receptors; they also have upregulated antiapoptotic gene expression, which can be differentially expressed within different areas of the same scar.

The underlying mechanisms that cause HTSs and keloids are not known. The immune system appears to be involved in the formation of both HTSs and keloids, although the exact relationship is unknown. Much is inferred from the presence of various immune cells in HTSs and keloids. For example, in both HTSs and keloids, keratinocytes express human leukocyte antigen (HLA)-2 and ICAM-1 receptors, which are absent in normal scar keratinocytes. Keloids also have increased deposition of immunoglobulins IgG, IgA, and IgM, and their formation correlates with serum levels of IgE. Antinuclear antibodies against fibroblasts, epithelial cells, and endothelial cells are found in keloids, but not HTSs. HTSs have higher T lymphocyte and Langerhans cell contents. There is also a larger number of mast cells present in both HTSs and keloids compared to normal scars. Another recently described cell population is the fibrocyte, a leukocyte subpopulation derived from peripheral mononuclear cells. Present in large numbers at the site of excess scarring, fibrocytes can stimulate fibroblast numbers and collagen synthesis. They also generate large numbers of cytokines, growth factors, and extracellular matrix proteins, which are characteristically upregulated in keloid tissue. Other mechanisms that may cause abnormal scarring include mechanical tension (although keloids often occur in areas of minimal tension) and prolonged irritation and/or inflammation that may lead to the generation of abnormal concentrations of profibrotic cytokines.

Treatment goals include restoration of function to the area, relief of symptoms, and prevention of recurrence. Many patients

seek intervention due to cosmetic concerns. Because the underlying mechanisms causing keloids and HTSs remain unknown, many different modalities of treatment have been used without consistent success.¹²¹

Excision alone of keloids is subject to a high recurrence rate, ranging from 45% to 100%. Inclusion of the dermal advancing edge that characterizes keloids, use of incisions in skin tension lines, and tension-free closure all have been proposed to decrease recurrence rates. There are fewer recurrences when surgical excision is combined with other modalities such as intralesional corticosteroid injection, topical application of silicone sheets, or the use of radiation or pressure. Surgery is recommended for debulking large lesions or as second-line therapy when other modalities have failed. Silicone application is relatively painless and should be maintained for 24 hours a day for about 3 months to prevent rebound hypertrophy. It may be secured with tape or worn beneath a pressure garment. The mechanism of action is not understood, but increased hydration of the skin, which decreases capillary activity, inflammation, hyperemia, and collagen deposition, may be involved. Silicone is more effective than other occlusive dressings and is an especially good treatment for children and others who cannot tolerate the pain involved in other modalities.¹⁰²

Intralesional corticosteroid injections decrease fibroblast proliferation, collagen and glycosaminoglycan synthesis, the inflammatory process, and TGF- β levels. When used alone, however, there is a variable rate of response and recurrence; therefore, steroids are recommended as first-line treatment for keloids and second-line treatment for HTSs if topical therapies have failed. Intralesional injections are more effective on younger scars. They may soften, flatten, and give symptomatic relief to keloids, but they cannot make the lesions disappear and they cannot narrow wide HTSs. Success is enhanced when used in combination with surgical excision. Serial injections every 2 to 3 weeks are required. Complications include skin atrophy, hypopigmentation, telangiectasias, necrosis, and ulceration.

Although radiation destroys fibroblasts, it has variable, unreliable results and produces poor results, with 10% to 100% recurrence when used alone. It is more effective when combined with surgical excision. The timing, duration, and dosage for radiation therapy are still controversial, but doses ranging from

1500 to 2000 rads appear effective. Given the risks of hyperpigmentation, pruritus, erythema, paresthesias, pain, and possible secondary malignancies, radiation should be reserved for adults with scars resistant to other modalities.

Pressure aids collagen maturation, flattens scars, and improves thinning and pliability. It reduces the number of cells in a given area, possibly by creating ischemia, which decreases tissue metabolism and increases collagenase activity. External compression is used to treat HTSs, especially after burns. Therapy must begin early, and a pressure between 24 and 30 mmHg must be achieved in order to exceed capillary pressure, yet preserve peripheral blood circulation. Garments should be worn for 23 to 24 hours a day for up to 1 or more years to avoid rebound hypertrophy. Scars older than 6 to 12 months respond poorly.

Topical retinoids also have been used as treatment for both HTSs and keloids, with reported responses of 50% to 100%. Intralesional injections of IFN- γ , a cytokine released by T lymphocytes, reduce collagen types I, II, and III by decreasing mRNA and possibly by reducing levels of TGF- β . As monotherapy, IFN- γ has failed because of high recurrence rates due to resistance to repeated injections. More recently, imiquimod, an immunomodulator that induces IFN- γ and other cytokines at the site of application, has been recommended following excision. Intralesional injections of chemotherapeutic agents such as 5-fluorouracil have been used both alone and in combination with steroids. The use of bleomycin or mitomycin C has been reported to achieve some success in older scars resistant to steroids.

Peritoneal Scarring. Peritoneal adhesions are fibrous bands of tissues formed between organs that are normally separated and/or between organs and the internal body wall. Most intra-abdominal adhesions are a result of peritoneal injury, either by a prior surgical procedure or due to intra-abdominal infection. Postmortem examinations demonstrate adhesions in 67% of patients with prior surgical procedures and in 28% with a history of intra-abdominal infection. Intra-abdominal adhesions are the most common cause (65%–75%) of small bowel obstruction, especially in the ileum. Operations in the lower abdomen have a higher chance of producing small bowel obstruction. Following rectal surgery, left colectomy, or total colectomy, there is an 11% chance of developing small bowel obstruction within 1 year, and this rate increases to 30% by 10 years. Adhesions also are a leading cause of secondary infertility in women and can cause substantial abdominal and pelvic pain. Adhesions account for 2% of all surgical admissions and 3% of all laparotomies in general surgery.¹²²

Adhesions form when the peritoneal surface is damaged due to surgery, thermal or ischemic injury, inflammation, or foreign body reaction. The injury disrupts the protective mesothelial cell layer lining the peritoneal cavity and the underlying connective tissue. The injury elicits an inflammatory response consisting of hyperemia, fluid exudation, release and activation of white blood cells and platelets in the peritoneal cavity, activation of inflammatory cytokines, and the onset of the coagulation and complement cascades. Fibrin deposition occurs between the damaged but opposed serosal surfaces. These filmy adhesions often are transient and degraded by proteases of the fibrinolytic system, with restoration of the normal peritoneal surface. If insufficient fibrinolytic activity is present, permanent fibrous adhesions will form by collagen deposition within 1 week of the injury (Fig. 9-12).

Extensive research has been done on the effect of surgery and peritonitis on the fibrinolytic and inflammatory cascades

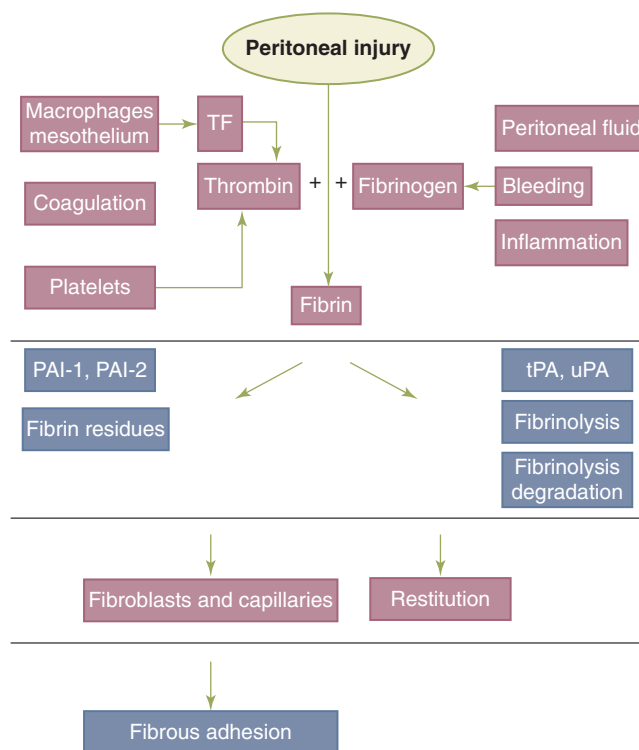


Figure 9-12. Fibrin formation and degradation in peritoneal tissue repair and adhesion formation. PAI-1, PAI-2 = types 1 and 2 plasminogen activator inhibitor; TF = tissue factor; tPA = tissue plasminogen activator; uPA = urokinase plasminogen activator.

within the peritoneal cavity. During normal repair, fibrin is principally degraded by the fibrinolytic protease plasmin, which is derived from inactive plasminogen through the action of two plasminogen activators (PA): tissue-type plasminogen activator (tPA) and urokinase-type plasminogen activator (uPA). Fibrinolytic activity in peritoneal fluid is reduced after abdominal surgery due to initial decreases in tPA levels and later to increases in plasminogen activator inhibitor-1 (PAI-1), which are induced by various cytokines, including TNF- α , IL-1, and interleukin-6 (IL-6).¹²³

There are two major strategies for adhesion prevention or reduction. Surgical trauma is minimized within the peritoneum by careful tissue handling, avoiding desiccation and ischemia, and spare use of cautery, laser, and retractors. Fewer adhesions form with laparoscopic surgical techniques due to reduced tissue trauma. The second major advance in adhesion prevention has been the introduction of barrier membranes and gels, which separate and create barriers between damaged mesothelial surfaces, allowing for adhesion-free healing. Currently, only three products are Food and Drug Administration (FDA) approved for reducing adhesion formation: Interceed® (oxidized regenerated cellulose, indicated only in pelvic surgery), Seprafilm® (a film composed of hyaluronic acid and carboxymethylcellulose) that is usually applied below the incision, and Adept® (4% icodextrin, a corn starch derivative in electrolyte solution, also for use mainly in pelvic surgery). However, use of these substances directly over bowel anastomoses is contraindicated due to an elevated risk of leak.¹²⁴ There have been innumerable studies investigating different molecules in hopes of preventing adhesion formation, but most of the success is limited to animal models, and clinically significant results in humans have yet to be achieved.

Local Care (Fig. 9-13)

Management of acute wounds begins with obtaining a careful history of the events surrounding the injury. The history is followed by a meticulous examination of the wound. Examination should assess the depth and configuration of the wound, the extent of nonviable tissue, and the presence of foreign bodies and other contaminants. Examination of the wound may require irrigation and débridement of the edges of the wound and is facilitated by use of local anesthesia. Antibiotic administration and tetanus prophylaxis may be needed, and planning the type and timing of wound repair should take place.

After completion of the history, examination, and administration of tetanus prophylaxis, the wound should be meticulously anesthetized. Lidocaine (0.5%–1%) or bupivacaine (0.25%–0.5%) combined with a 1:100,000 to 1:200,000 dilution of epinephrine provides satisfactory anesthesia and hemostasis. Epinephrine should not be used in wounds of the fingers, toes, ears, nose, or penis, due to the risk of tissue necrosis secondary to terminal arteriole vasospasm in these structures. Injection of these anesthetics can result in significant initial patient discomfort, and this can be minimized by slow injection, infiltration of the subcutaneous tissues, and buffering the solution with sodium bicarbonate. Care must be observed in calculating the maximum dosages of lidocaine or bupivacaine in order to avoid toxicity-related side effects.

Irrigation to visualize all areas of the wound and remove foreign material is best accomplished with normal saline (without additives). High-pressure wound irrigation is more effective in achieving complete débridement of foreign material and nonviable tissues. Iodine, povidone-iodine, hydrogen peroxide, and organically based antibacterial preparations have all been shown to impair wound healing due to injury to wound neutrophils and macrophages, and thus should not be used. All hematomas present within wounds should be carefully evacuated and any remaining bleeding sources controlled with ligature or cautery. If the injury has resulted in the formation of a marginally viable flap of skin or tissue, this should be resected or revascularized prior to further wound repair and closure.

After the wound has been anesthetized, explored, irrigated, and débrided, the area surrounding the wound should be cleaned, inspected, and the surrounding hair clipped. The area surrounding the wound should be prepared with povidone iodine, chlorhexidine, or similar bacteriostatic solutions and draped with sterile towels. Having ensured hemostasis and adequate débridement of nonviable tissues and removal of any remaining foreign bodies, irregular, macerated, or beveled wound edges should be débrided in order to provide a fresh edge for reapproximation. Although plastic surgical techniques such as W- or Z-plasty are seldom recommended for acute wounds, great care must be taken to realign wound edges properly. This is particularly important for wounds that cross the vermilion border, eyebrow, or hairline. Initial sutures that realign the edges of these different tissue types will speed and greatly enhance the aesthetic outcome of the wound repair.

In general, the smallest suture required to hold the various layers of the wound in approximation should be selected in order to minimize suture-related inflammation. Nonabsorbable or slowly absorbing monofilament sutures are most suitable for approximating deep fascial layers, particularly in the abdominal wall. Subcutaneous tissues should be closed with braided absorbable sutures, with care to avoid placement of sutures in fat. Although traditional teaching in wound closure has emphasized multiple-layer closures, additional layers of suture closure are associated with increased risk of wound infection, especially when placed in fat. Drains may be placed in areas at risk of forming fluid collections.

In areas of significant tissue loss, rotation of adjacent musculocutaneous flaps may be required to provide sufficient tissue mass for closure. These musculocutaneous flaps may be based on intrinsic blood supply or may be moved from distant sites as free flaps and anastomosed into the local vascular bed. In areas with significant superficial tissue loss, split-thickness skin grafting (placed in a delayed manner to assure an adequate tissue bed) may be required and will speed formation of an intact epithelial barrier to fluid loss and infection. Split-thickness skin grafts are readily obtained using manual or mechanical dermatomes, and the grafts may be “meshed” in order to increase the surface area of their coverage. It is essential to ensure hemostasis

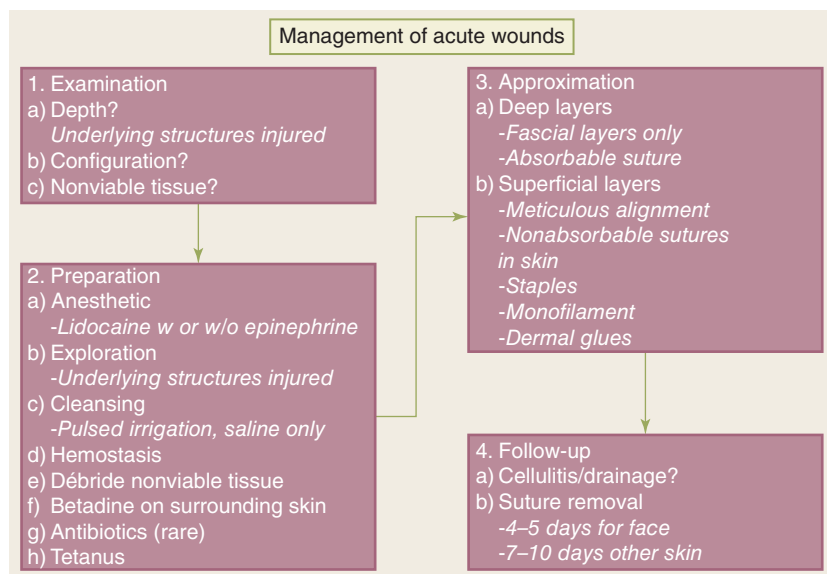


Figure 9-13. Algorithm for management of acute wounds.

of the underlying tissue bed prior to placement of split-thickness skin grafts, as the presence of a hematoma below the graft will prevent the graft from taking, resulting in sloughing of the graft. In acute, contaminated wounds with skin loss, use of porcine skin xenografts or skin cadaveric allografts is prudent until the danger of infection passes.

After closing deep tissues and replacing significant tissue deficits, skin edges should be reapproximated for cosmesis and to aid in rapid wound healing. Skin edges may be quickly reapproximated with stainless steel staples or nonabsorbable monofilament sutures. Care must be taken to remove these from the wound prior to epithelialization of the skin tracts where sutures or staples penetrate the dermal layer. Failure to remove the sutures or staples prior to 7 to 10 days after repair will result in a cosmetically inferior wound. Where wound cosmesis is important, the above problems may be avoided by placement of buried dermal sutures using absorbable braided sutures. This method of wound closure allows for a precise reapproximation of wound edges and may be enhanced by application of wound closure tapes to the surface of the wound. Intradermal absorbable sutures do not require removal. Use of skin tapes alone is only recommended for closure of the smallest superficial wounds. Larger wounds generate sufficient lateral tension that the epithelial edges either separate or curl upward under the tapes, resulting in inadequate epithelial apposition and poor cosmesis.

The development of octyl-cyanoacrylate tissue glues have shown new promise for the management of simple, linear wounds with viable skin edges. These new glues are less prone to brittleness and have superior burst-strength characteristics. Studies have shown them to be suitable for use in contaminated situations without significant risk of infection. When used in the above types of wounds, these glues appear to provide superb cosmetic results and result in significantly less trauma than sutured repair, particularly when used in pediatric patients.

Antibiotics

Antibiotics should be used only when there is an obvious wound infection. Most wounds are contaminated or colonized with bacteria. The presence of a host response constitutes an infection and justifies the use of antibiotics. Signs of infection to look for include erythema, cellulitis, swelling, and purulent discharge. Indiscriminate use of antibiotics should be avoided to prevent emergence of multidrug-resistant bacteria.

Antibiotic treatment of acute wounds must be based on organisms suspected to be found within the infected wound and the patient's overall immune status. When a single specific organism is suspected, treatment may be commenced using a single antibiotic. Conversely, when multiple organisms are suspected, as with enteric contamination or when a patient's immune function is impaired by diabetes, chronic disease, or medication, treatment should commence with a broad-spectrum antibiotic or several agents in combination. Lastly, the location of the wound and the quality of tissue perfusion to that region will significantly impact wound performance after injury. Antibiotics also can be delivered topically as part of irrigations or dressings, although their efficacy is questionable.

Dressings

The main purpose of wound dressings is to provide the ideal environment for wound healing. The dressing should facilitate the major changes taking place during healing to produce an optimally

Table 9-9

Desired characteristics of wound dressings

Promote wound healing (maintain moist environment)
Conformability
Pain control
Odor control
Nonallergenic and nonirritating
Permeability to gas
Safety
Nontraumatic removal
Cost-effectiveness
Convenience

healed wound. Although the ideal dressing still is not a clinical reality, technological advances are promising (Table 9-9).

Covering a wound with a dressing mimics the barrier role of epithelium and prevents further damage. In addition, application of compression provides hemostasis and limits edema. Occlusion of a wound with dressing material helps healing by controlling the level of hydration and oxygen tension within the wound. It also allows transfer of gases and water vapor from the wound surface to the atmosphere. Occlusion affects both the dermis and epidermis, and it has been shown that exposed wounds are more inflamed and develop more necrosis than covered wounds. Occlusion also helps in dermal collagen synthesis and epithelial cell migration and limits tissue desiccation. Since it may enhance bacterial growth, occlusion is contraindicated in infected and/or highly exudative wounds.

Dressings can be classified as primary or secondary. A primary dressing is placed directly on the wound and may provide absorption of fluids and prevent desiccation, infection, and adhesion of a secondary dressing. A secondary dressing is one that is placed on the primary dressing for further protection, absorption, compression, and occlusion. Many types of dressings exist and are designed to achieve certain clinically desired endpoints.

Absorbent Dressings. Accumulation of wound fluid can lead to maceration and bacterial overgrowth. Ideally, the dressing should absorb without getting soaked through, as this would permit bacteria from the outside to enter the wound. The dressing must be designed to match the exudative properties of the wound and may include cotton, wool, and sponge.

Nonadherent Dressings. Nonadherent dressings are impregnated with paraffin, petroleum jelly, or water-soluble jelly for use as nonadherent coverage. A secondary dressing must be placed on top to seal the edges and prevent desiccation and infection.

Occlusive and Semiocclusive Dressings. Occlusive and semiocclusive dressings provide a good environment for clean, minimally exudative wounds. These film dressings are waterproof and impervious to microbes but permeable to water vapor and oxygen.

Hydrophilic and Hydrophobic Dressings. These dressings are components of a composite dressing. Hydrophilic dressing aids in absorption, whereas a hydrophobic dressing is waterproof and prevents absorption.

Hydrocolloid and Hydrogel Dressings. Hydrocolloid and hydrogel dressings attempt to combine the benefits of occlusion and absorbency. Hydrocolloids and hydrogels form complex

structures with water, and fluid absorption occurs with particle swelling, which aids in atraumatic removal of the dressing. Absorption of exudates by the hydrocolloid dressing leaves a yellowish-brown gelatinous mass after dressing removal that can be washed off. Hydrogel is a cross-linked polymer that has high water content. Hydrogels allow a high rate of evaporation without compromising wound hydration, which makes them useful in burn wound treatment.

Alginates. Alginates are derived from brown algae and contain long chains of polysaccharides containing mannuronic and glucuronic acid. The ratios of these sugars vary with the species of algae used, as well as the season of harvest. Processed as the calcium form, alginates turn into soluble sodium alginate through ion exchange in the presence of wound exudates. The polymers gel, swell, and absorb a great deal of fluid. Alginates are being used when there is skin loss, in open surgical wounds with medium exudation, and on full-thickness chronic wounds.

Absorbable Materials. Absorbable materials are mainly used within wounds as hemostats and include collagen, gelatin, oxidized cellulose, and oxidized regenerated cellulose.

Medicated Dressings. Medicated dressings have long been used as a drug-delivery system. Agents delivered in the dressings include benzoyl peroxide, zinc oxide, neomycin, and bacitracin-zinc. These agents have been shown to increase epithelialization by 28%.

The type of dressing to be used depends on the amount of wound drainage. A nondraining wound can be covered with semioclusive dressing. Drainage of less than 1 to 2 mL/d may require a semioclusive or absorbent nonadherent dressing. Moderately draining wounds (3–5 mL/d) can be dressed with a nonadherent primary layer plus an absorbent secondary layer plus an occlusive dressing to protect normal tissue. Heavily draining wounds (>5 mL/d) require a similar dressing as moderately draining wounds, but with the addition of a highly absorbent secondary layer.

Mechanical Devices. Mechanical therapy augments and improves on certain functions of dressings, in particular the absorption of exudates and control of odor. The vacuum-assisted closure (VAC) system assists in wound closure by applying localized negative pressure to the surface and margins of the wound. The negative-pressure therapy is applied to a special foam dressing cut to the dimensions of the wound and positioned in the wound cavity or over a flap or graft. The continuous negative pressure is very effective in removing exudates from the wound. This form of therapy has been found to be effective for chronic open wounds (diabetic ulcers and stages III and IV pressure ulcers), acute and traumatic wounds,¹²⁵ flaps and grafts, and subacute wounds (i.e., dehiscent incisions), although more randomized trials need to be carried out to confirm efficacy.

Skin Replacements

All wounds require coverage in order to prevent evaporative losses and infection and to provide an environment that promotes healing. Both acute and chronic wounds may demand use of skin replacement, and several options are available.

Conventional Skin Grafts. Skin grafts have long been used to treat both acute and chronic wounds. Split- (partial-) thickness grafts consist of the epidermis plus part of the dermis, whereas full-thickness grafts retain the entire epidermis and dermis. Autologous grafts (autografts) are transplants from one site on the body to another; allogeneic grafts (allografts, homografts)

are transplants from a living nonidentical donor or cadaver to the host; and xenogeneic grafts (heterografts) are taken from another species (e.g., porcine). Split-thickness grafts require less blood supply to restore skin function. The dermal component of full-thickness grafts lends mechanical strength and resists wound contraction better, resulting in improved cosmesis. Allogeneic and xenogeneic grafts require the availability of tissue, are subject to rejection, and may contain pathogens.

The use of skin grafts or bioengineered skin substitutes and other innovative treatments (e.g., topically applied growth factors, systemic agents, and gene therapy) cannot be effective unless the wound bed is adequately prepared. This may include débridement to remove necrotic or fibrinous tissue, control of edema, revascularization of the wound bed, decreasing the bacterial burden, and minimizing or eliminating exudate. Temporary placement of allografts or xenografts may be used to prepare the wound bed.

Skin Substitutes. Originally devised to provide coverage of extensive wounds with limited availability of autografts, skin substitutes also have gained acceptance as natural dressings. Manufactured by tissue engineering, they combine novel materials with living cells to provide functional skin substitutes, providing a bridge between dressings and skin grafts.

Skin substitutes have theoretical advantages of being readily available and not requiring painful harvest, and they may be applied freely or with surgical suturing. In addition, they promote healing, either by stimulating host cytokine generation or by providing cells that may also produce growth factors locally. Their disadvantages include limited survival, high cost, and the need for multiple applications (Table 9-10). Allografting, albeit with a very thin graft, may at times be required to accomplish complete coverage.

A variety of skin substitutes are available, each with its own set of advantages and disadvantages; however, the ideal skin substitute has yet to be developed (Table 9-11). The development of the newer composite substitutes, which provide both the dermal and epidermal components essential for permanent skin replacement, may represent an advance toward that goal. The acellular (e.g., native collagen or synthetic material) component acts as a scaffold, promotes cell migration and growth, and activates tissue regeneration and remodeling. The cellular elements re-establish lost tissue and associated function, synthesize extracellular matrix components, produce essential mediators such as cytokines and growth factors, and promote proliferation and migration.

Cultured epithelial autografts (CEAs) represent expanded autologous or homologous keratinocytes. CEAs are expanded from a biopsy of the patient's own skin, will not be rejected,

Table 9-10

Desired features of tissue-engineered skin

Rapid re-establishment of functional skin (epidermis/dermis)
Receptive to body's own cells (e.g., rapid "take" and integration)
Graftable by a single, simple procedure
Graftable on chronic or acute wounds
Engraftment without use of extraordinary clinical intervention (i.e., immunosuppression)

Table 9-11

Advantages and disadvantages of various bioengineered skin substitutes

SKIN SUBSTITUTE	ADVANTAGES	DISADVANTAGES
Cultured allogeneic keratinocyte graft	No biopsy needed “Off the shelf” availability Provides wound coverage Promotes healing	Unstable Does not prevent wound contracture Inadequate cosmesis Possibility of disease transmission Fragile
Bioengineered dermal replacement	Prevents contracture Good prep for graft application	Limited ability to drive re-epithelialization Largely serves as temporary dressing
Cultured bilayer skin equivalent	More closely mimics normal anatomy Does not need secondary procedure Easily handled Can be sutured, meshed, etc.	Cost Short shelf life True engraftment questionable

and can stimulate re-epithelialization as well as the growth of underlying connective tissue. Keratinocytes harvested from a biopsy roughly the size of a postage stamp are cultured with fibroblasts and growth factors and grown into sheets that can cover large areas and give the appearance of normal skin. Until the epithelial sheets are sufficiently expanded, the wound must be covered with an occlusive dressing or a temporary allograft or xenograft. The dermis regenerates very slowly, if at all, for full-thickness wounds, because the sheets are very fragile, are difficult to work with, are susceptible to infection, and do not resist contracture well, leading to poor cosmetic results.

CEAs are available from cadavers, unrelated adult donors, or neonatal foreskins. Fresh or cryopreserved cultured allogeneic keratinocytes can be left in place long enough to be superseded by multiplying endogenous skin cells because, unlike allografts containing epidermal Langerhans cells, they do not express major histocompatibility antigens. Cryopreserved CEAs are readily available “off the shelf,” and provide growth factors that may aid healing. However, like autologous keratinocyte sheets, the grafts lack the strength provided by a dermal component and pose a risk of disease transmission.

Viable fibroblasts can be grown on bioabsorbable or non-bioabsorbable meshes to yield living dermal tissue that can act as a scaffold for epidermal growth. Fibroblasts stimulated by growth factors can produce type I collagen and glycosaminoglycans (e.g., chondroitin sulfates), which adhere to the wound surface to permit epithelial cell migration, as well as adhesive ligands (e.g., the matrix protein fibronectin), which promote cell adhesion. This approach has the virtue of being less time-consuming and expensive than culturing keratinocyte sheets. There are a number of commercially available, bioengineered dermal replacements approved for use in burn wound treatment as well as other indications.

Bioengineered skin substitutes have evolved from keratinocyte monolayers to dermal equivalents to split-thickness products with a pseudo-epidermis, and most recently, to products containing both epidermal and dermal components that resemble the three-dimensional structure and function of normal skin (see Table 9-11). Indicated for use with standard compression therapy in the treatment of venous insufficiency ulcers and for the treatment of neuropathic diabetic foot ulcers, these bilayered skin equivalents also are being used in a variety of wound care settings.

Growth Factor Therapy. As discussed previously, it is believed that nonhealing wounds result from insufficient or inadequate growth factors in the wound environment. A simplistic solution would be to flood the wound with single or multiple growth factors in order to “jump-start” healing and re-epithelialization. Although there is a large body of work demonstrating the effects of growth factors in animals, translation of these data into clinical practice has met with limited success. Growth factors for clinical use may be either recombinant or homologous/autologous. Autologous growth factors are harvested from the patient’s own platelets, yielding an unpredictable combination and concentration of factors, which are then applied to the wound. This approach allows treatment with patient-specific factors at an apparently physiologic ratio of growth factor concentrations. Disappointingly, a recent meta-analysis failed to demonstrate any value for autologous platelet-rich plasma in the treatment of chronic wounds.¹²⁶ Recombinant molecular biologic means permit the purification of high concentrations of individual growth factors. Current FDA-approved formulations, as well as those used experimentally, deliver concentrations approximately 10^3 times higher than those observed physiologically.

At present, only platelet-derived growth factor BB (PDGF-BB) is currently approved by the FDA for treatment of diabetic foot ulcers. Application of recombinant human PDGF-BB in a gel suspension to these wounds increases the incidence of total healing and decreases healing time. Several other growth factors have been tested clinically and show some promise, but currently none are approved for use. A great deal more needs to be discovered about the concentration, temporal release, and receptor cell population before growth factor therapy is to make a consistent impact on wound healing.

Gene or Cell Therapy. Given the disappointing results from the application of purified growth factors onto wounds, the possible therapeutic potential of gene therapy has been recognized and studied. Direct access to the open wound bed, which characterizes almost all chronic wounds, has facilitated this therapy. Gene delivery to wounds includes traditional approaches such as viral vectors and plasmid delivery or, more recently, electroporation and microseeding.

Although a variety of genes expressing interleukin-8, PDGF, IGF-1, keratinocyte growth factor, and laminin-5 have

been successfully delivered to wounds in both animal and human models, the effects have been modest and specific to unique wound situations. Delivering *extra* genes into the wound bed presents the challenge of expression of the necessary signals to turn the genes on and off at appropriate times so that dys-regulated, hypertrophic, and abnormal healing does not occur. Elaborate systems have been created for topical use as on/off switches for genes. The more important question is which genes to express, in what temporal sequence, and in what regions of the wound bed, as it is unlikely that a single gene coding for one protein can significantly affect overall healing. There is growing consensus that delivery of genes is not going to represent the universal solution. Although gene therapy replaces missing or defective genes, most acute wounds already have and express the necessary genes for successful healing and the wound environment produces signals adequate to the activation of these genes. What, if any, are the deficiencies in gene expression or activity in failed wounds is unknown.

Another approach is to deliver multiple genes coding for proteins that can act synergistically and even in a timed sequence, as would occur during normal healing. This would involve the use of activated cells that participate in the healing sequence that could be delivered in an activated state to the wound environment. Use of mesenchymal stem cells as a delivery vector for many genes simultaneously is the latest such approach. The feasibility of applying bone marrow-derived, umbilical cord-derived, adipose-derived, and epidermal stem cells that can differentiate into various cells that participate in the wound healing response also has been documented. These cells, as part of their differentiation and activation in the wound, have been shown to produce a variety of growth factors including VEGF, PDGF, bFGF, and MMP-9. The challenges remain how to maintain the viability and activity of the transplanted cells, how to document that the observed effects are due to the delivered cells, and what are the mechanisms necessary for regulating or ending their activity.

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10 chapter

Oncology

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ONCOLOGY AND SURGICAL PRACTICE

As the population ages, oncology is becoming a larger portion of surgical practice. The surgeon often is responsible for the initial diagnosis and management of solid tumors. Knowledge of cancer epidemiology, etiology, staging, and natural history is required for initial patient assessment, as well as to determination of the optimal surgical therapy.

Modern cancer therapy is multidisciplinary, involving the coordinated care of patients by surgeons, medical oncologists, radiation oncologists, reconstructive surgeons, pathologists, radiologists, and primary care physicians. **Primary** (or **1► definitive**) *surgical therapy* refers to en bloc resection of tumor with adequate margins of normal tissues and regional lymph nodes as necessary. *Adjuvant therapy* refers to radiation therapy and systemic therapies, including chemotherapy,

immunotherapy, hormonal therapy, and, increasingly, biologic therapy. The primary goal of surgical and radiation therapy is local and regional control. On the other hand, the primary goal of systemic therapy is systemic control by treatment of distant foci of subclinical disease to prevent distant recurrence. Surgeons must be familiar with adjuvant therapies to coordinate multidisciplinary care and to determine the best sequence of therapy.

Recent advances in molecular biology are revolutionizing medicine. New information is being translated rapidly into clinical use, with the development of new prognostic and predictive markers and new biologic therapies. Increasingly cancer therapy is getting personalized, incorporating information about each patient's tumor characteristics, patient's own genome, as well as host immune responses and tumor microenvironment, into clinical decision-making. It is therefore essential that surgeons

Key Points

- 1► Modern cancer therapy is multidisciplinary, involving coordinated care by surgeons, medical oncologists, radiation oncologists, reconstructive surgeons, pathologists, radiologists, and primary care physicians.
- 2► Understanding cancer biology is essential to successfully implement personalized cancer therapy.

- 3► The following alterations are critical for malignant cancer growth: self-sufficiency of growth signals, insensitivity to growth-inhibitory signals, evasion of apoptosis, potential for limitless replication, angiogenesis, invasion and metastasis. Reprogramming of energy metabolism and evading immune destruction.

understand the principles of molecular oncology to appropriately interpret these new contributions and incorporate them into practice.

EPIDEMIOLOGY

Basic Principles of Cancer Epidemiology

The term *incidence* refers to the number of new cases occurring. Incidence is usually expressed as the number of new cases per 100,000 persons per year. *Mortality* refers to the number of deaths occurring and is expressed as the number of deaths per 100,000 persons per year. Incidence and mortality data are usually available through cancer registries. Mortality data are also available as public records in many countries where deaths are registered as vital statistics, often with the cause of death. In areas where cancer registries do not exist, mortality data are used to extrapolate incidence rates. These numbers are likely to be less accurate than registry data, as the relationship between incidence and cause-specific death is likely to vary significantly among countries owing to the variation in health care delivery.

The incidence of cancer varies by geography. This is due in part to genetic differences and in part to differences in environmental and dietary exposures. Epidemiologic studies that monitor trends in cancer incidence and mortality have tremendously enhanced our understanding of the etiology of cancer. Furthermore, analysis of trends in cancer incidence and mortality allows us to monitor the effects of different preventive and screening measures, as well as the evolution of therapies for specific cancers.

The two types of epidemiologic studies that are conducted most often to investigate the etiology of cancer and the effect of prevention modalities are cohort studies and case-control studies. Cohort studies follow a group of people who initially do not have a disease over time and measure the rate of development of a disease. In cohort studies, a group that is exposed to a certain environmental factor or intervention usually is compared to a group that has not been exposed (e.g., smokers vs. nonsmokers). Case-control studies compare a group of patients affected with a disease to a group of individuals without the disease for a given exposure. The results are expressed in terms of an odds ratio, or relative risk. A relative risk <1 indicates a protective effect of the exposure, whereas a relative risk >1 indicates an increased risk of developing the disease with exposure.

Cancer Incidence and Mortality in the United States

In the year 2013, it is estimated that 1.6 million new cancer cases will be diagnosed in the United States, excluding carcinoma in situ of any site except bladder, and excluding basal cell and squamous cell carcinomas of the skin.¹ In addition,

64,640 cases of carcinoma in situ of the breast, and 61,300 of melanoma in situ are expected.¹

It is estimated that in 2013 estimated 580,350 people will die of cancer in the United States, corresponding to about 1600 deaths per day.¹ The estimated new cancer cases and deaths by cancer type are shown in Table 10-1.¹ The most common causes of cancer death in men are cancers of the lung and bronchus, prostate, and colon and rectum; in women, cancers are of the lung and bronchus, breast, and colon and rectum.¹ These four cancers account for almost half (48%) of total cancer deaths among men and women.

The annual age-adjusted cancer incidence rates among males and females for selected cancer types are shown in Fig. 10-1.¹ Incidence rates are declining for most cancer sites, but they are increasing among both men and women for melanoma of the skin, cancers of the liver and thyroid (Fig. 10-2).¹ Incidence rates are decreasing for all four major cancer sites except for breast cancer in women. Age-adjusted incidence rate of breast cancer started to decrease from 2001 to 2004.² This decrease in breast cancer incidence has at least temporally been associated with the first report of the Women's Health Initiative, which documented an increased risk of coronary artery disease and breast cancer with the use of hormone replacement therapy; this was followed by a drop in the use of hormone replacement therapy by postmenopausal women in the United States.² Unfortunately after this initial drop, breast cancer incidence has remained relatively stable from 2005 to 2009.

Declines in colorectal cancer incidence have been mainly attributed to increased screening that allows for removal of precancerous polyps. Prostate cancer rates rapidly increased and decreased between 1995 and 1998. These trends are thought to be attributable to increased use of prostate-specific antigen (PSA) screening.³ Although analysis now suggest prostate cancer incidence has declined steadily by 1.9% per year from 2000 to 2009, annual rates fluctuate likely reflecting variations in screening.

Differences in lung cancer incidence patterns between women and men are thought to reflect historical differences in tobacco use. Differences in smoking prevalence is also thought to contribute to regional differences in lung cancer incidence. Lung cancer incidence is fourfold higher in Kentucky which has the highest smoking prevalence, compared with Utah, that has the lowest smoking prevalence (128 vs. 34 lung cancer cases per 100,000 men).¹

The 5-year survival rates for selected cancers are listed in Table 10-2. From 2005 to 2009, cancer death rates decreased by 1.8% per year in males and by 1.5% per year in females.¹ These declines in mortality have been consistent in the past decade, and larger than what was observed in the previous decade.³ Over the past two decades, death rates have decreased from their peak by more than 30% for colorectal cancer, female breast cancer,

Table 10-1

Estimated new cancer cases and deaths, United States, 2013^a

	ESTIMATED NEW CASES	ESTIMATED DEATHS		ESTIMATED NEW CASES	ESTIMATED DEATHS
All cancers	1,660,290	580,350	Genital system	339,810	58,480
Oral cavity and pharynx	41,380	7,890	Uterine cervix	12,340	4,030
Digestive system	290,200	144,570	Uterine corpus	49,560	8,190
Esophagus	17,990	15,210	Ovary	22,240	14,030
Stomach	21,600	10,990	Vulva	4,700	990
Small intestine	8,810	1,170	Vagina and other genital, female	2,890	840
Colon and rectum	142,820	50,830	Prostate	238,590	29,720
Anus, anal canal, and anorectum	7,060	880	Testis	7,920	370
Liver and intrahepatic bile duct	30,640	21,670	Penis and other genital, male	1,570	310
Gallbladder and other biliary	10,310	3,230	Urinary system	140,430	29,790
Pancreas	45,220	38,460	Urinary bladder	72,570	15,210
Other digestive organs	5,750	2,130	Kidney and renal pelvis	65,150	13,680
Respiratory system	246,210	163,890	Ureter and other urinary organs	2,710	900
Larynx	12,260	3,630	Eye and orbit	2,800	320
Lung and bronchus	228,190	159,480	Brain and other nervous system	23,130	14,080
Other respiratory organs	5,760	780	Endocrine system	62,710	2,770
Bones and joints	3,010	1,440	Thyroid	60,220	1,850
Soft tissue (including heart)	11,410	4,390	Other endocrine	2,490	920
Skin (excluding basal and squamous)	82,770	12,650	Lymphoma	79,030	20,200
Melanoma	76,690	9,480	Multiple myeloma	22,350	10,710
Other nonepithelial	6,080	3,170	Leukemia	48,610	23,720
Breast	234,580	40,030	Other and unspecified primary sites^b	31,860	45,420

^aExcludes basal and squamous cell skin cancers and in situ carcinomas except those of urinary bladder.

^bMore deaths than cases suggest lack of specificity in recording underlying causes of death on death certificate.

Source: Modified with permission from John Wiley and Sons: Siegel R et al. *Cancer statistics, 2013*. CA: a cancer journal for clinicians. 2013;63:11. © 2013 American Cancer Society, Inc.

male lung cancer and more than 40% for prostate cancer. The decrease in lung cancer death rates in men is thought to be due to a decrease in tobacco use, whereas the decreases in death rates from breast, colorectal cancer, and prostate cancer reflect advances in early detection and treatment.

Global Statistics on Cancer Incidence and Mortality

The five most common cancers for men worldwide are lung, prostate, colorectal cancer, stomach, liver, and for women are breast, colorectal, cervix, lung, and stomach.⁴ Notably, for several cancer types there is wide geographical variability in cancer incidence (Fig. 10-3). The mortality rates for different cancers also vary significantly among countries. This is attributable not only to variations in incidence but also to variations in survival after a cancer diagnosis. The survival rates are influenced by treatment patterns as well as by variations in cancer screening practices, which affect the stage of cancer at diagnosis. For example, the 5-year survival rate for stomach cancer is much higher in Japan, where the cancer incidence is high enough to

warrant mass screening, which is presumed to lead to earlier diagnosis. In the case of prostate cancer, on the other hand, the mortality rates diverge much less than the incidence rates among countries. Survival rates for prostate cancer are much higher in North America than in developing countries.⁵ It is possible that the extensive screening practices in the United States allow discovery of cancers at an earlier, more curable stage; however, it is also possible that this screening leads to discovery of more latent, less biologically aggressive cancers, which may not have caused death even if they had not been identified.

About one million new cases of stomach cancer were estimated to have occurred in 2008 (988,000 cases, 7.8% of the total), making it the fourth most common malignancy in the world, behind cancers of the lung, breast, and colorectal cancer. The incidence of stomach cancer varies significantly among different regions of the world. The difference in risk by country is presumed to be primarily due to differences in dietary factors. The risk is increased by high consumption of preserved salted foods such as meats and pickles, and decreased by high intake of fruits and vegetables.⁵ There also is some international variation

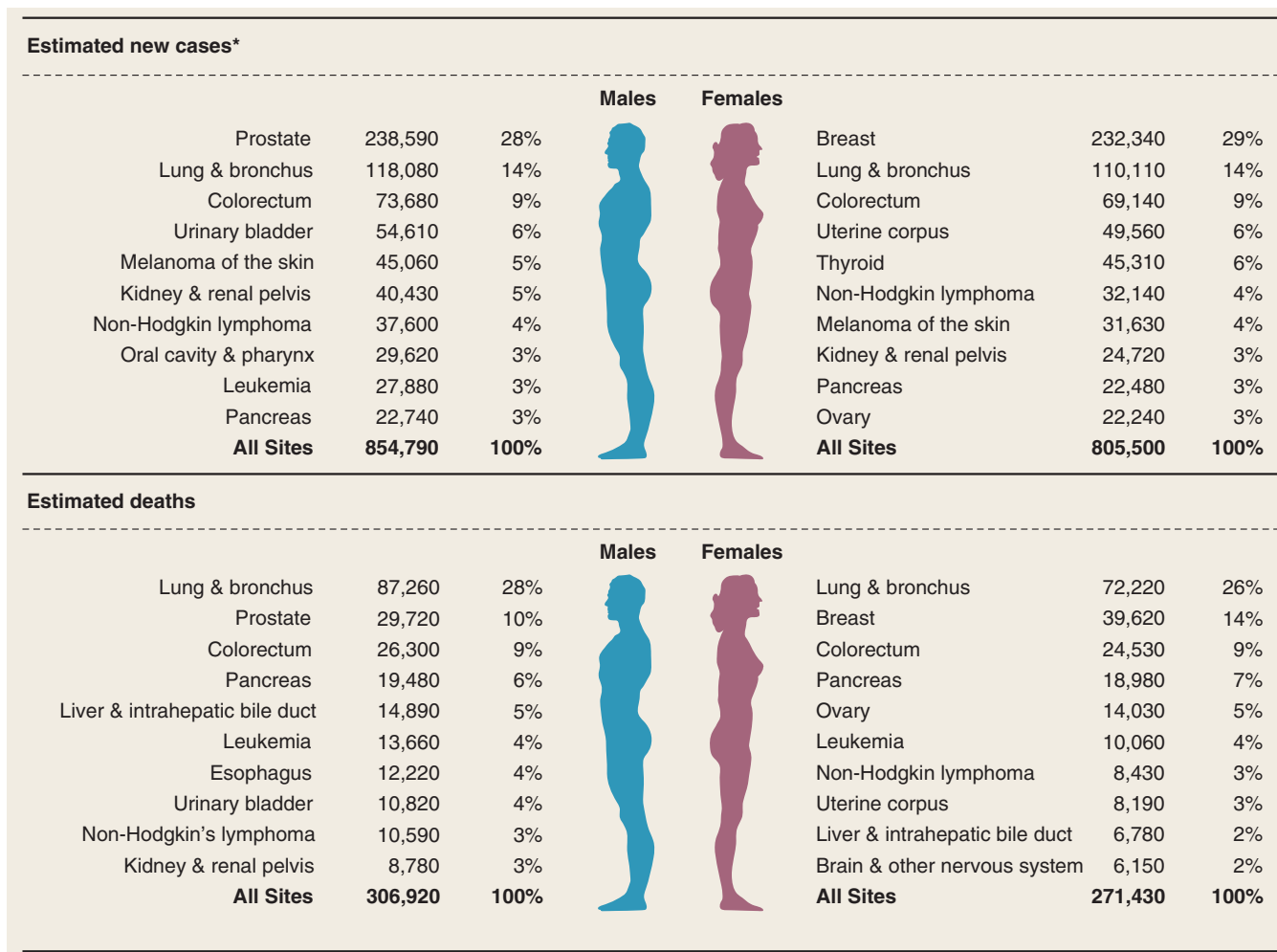


Figure 10-1. Ten leading cancer types with the estimated new cancer cases and deaths by sex in the United States, 2013. *Excludes basal and squamous cell skin cancers and in situ carcinomas except those of the urinary bladder. Estimates are rounded to the nearest 10 (Modified with permission from John Wiley and Sons: Siegel R et al. Cancer statistics, 2013. CA: a cancer journal for clinicians. 2013;63:11. © 2013 American Cancer Society, Inc.)

in the incidence of infection with *Helicobacter pylori*, which is known to play a major role in gastric cancer development.⁵ Fortunately, a steady decline is being observed in the incidence and mortality rates of gastric cancer. This may be related to improvements in preservation and storage of foods as well as due to changes in the prevalence of *H. pylori*.⁵ More than 70% of cases (713,000 cases) occur in developing countries, and half the cases in the world occur in Eastern Asia (mainly in China).⁴ Age-standardized incidence rates are about twice as high for men as for women, ranging from 3.9 in Northern Africa to 42.4 in Eastern Asia for men, and from 2.2 in Southern Africa to 18.3 in Eastern Asia for women. Stomach cancer is the second leading cause of cancer death in both sexes worldwide.

Overall, the incidence of breast cancer is rising in most countries. Incidence varies from 19.3 per 100,000 women in Eastern Africa to 89.7 per 100,000 women in Western Europe, and are high in developed regions of the world (except Japan) and low in most of the developing regions.⁴ Although breast cancer has been linked to cancer susceptibility genes, mutations in these genes account for only 5% to 10% of breast tumors, which suggests that the wide geographic variations in breast cancer incidence are not due to geographic variations in the prevalence of these genes. Most of the differences, therefore, are attributed to differences in reproductive factors, diet, alcohol,

obesity, physical activity, and other environmental differences. Indeed, breast cancer risk increases significantly in females who have migrated from Asia to America.⁵ The range of breast cancer mortality rates is much less (approximately 6 to 19 per 100,000) because of the more favorable survival of breast cancer in developed regions. As a result, breast cancer ranks as the fifth cause of death from cancer overall (458,000 deaths), but it is still the most frequent cause of cancer death in women in both developing (269,000 deaths, 12.7% of total) and developed regions (estimated 189,000 deaths).⁴

There is a 25-fold variation in colon cancer incidence worldwide.⁵ The incidence of colon and rectal cancer is higher in developed countries than in developing countries. The incidence rates are highest in North America, Australia and New Zealand, and Western Europe, and especially in Japanese men.⁵ In contrast, the incidence is relatively low in North Africa, South America, and eastern, Southeastern, and Western Asia. These geographic differences are thought to reflect environmental exposures and are presumed to be related mainly to dietary differences in consumption of animal fat, meat, and fiber.⁵

Worldwide liver cancer is the fifth most common cancer in men (523,000 cases, 7.9% of the total) and the seventh in women (226,000 cases, 6.5% of the total). Almost 85% of liver cancer cases occur in developing countries, and particularly in men.⁴

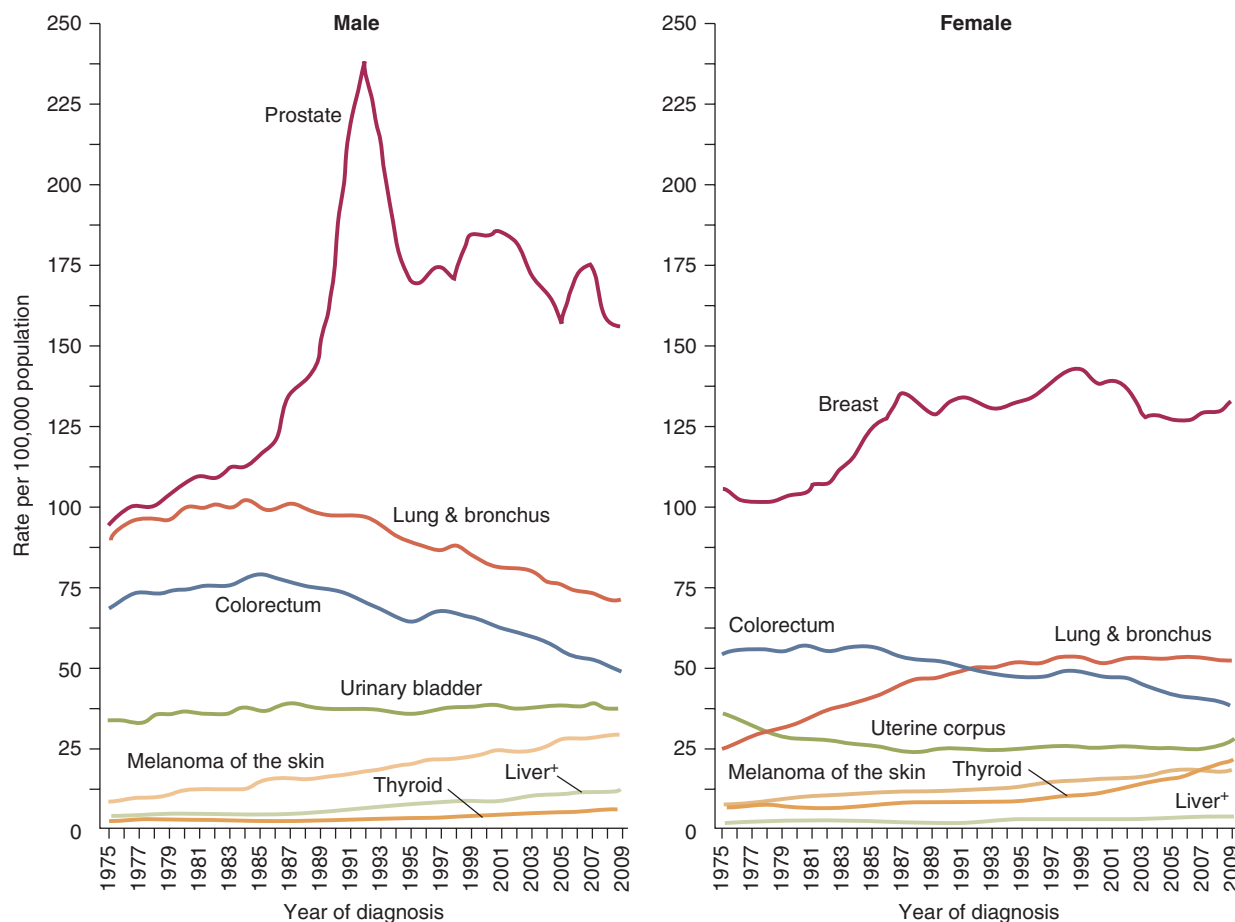


Figure 10-2. Trends in cancer incidence rates for selected cancer by sex among males and females for selected cancer types, United States, 1975 to 2009. Rates are age adjusted to the 2000 U.S. standard population. (Modified with permission from John Wiley and Sons: Siegel R et al. Cancer statistics, 2013. *CA: a cancer journal for clinicians*. 2013;63:11. © 2013 American Cancer Society, Inc.)¹

*Liver includes intrahepatic bile duct

The overall sex ratio male:female is 2:4. The regions of high incidence are Eastern and Southeastern Asia, Middle and Western Africa, as well as Melanesia and Micronesia/Polynesia (particularly in men). Low rates are estimated in developed regions, with the exception of Southern Europe. There were an estimated 694,000 deaths from liver cancer in 2008 (477,000 in men, 217,000 in women), and because of its high fatality (overall ratio of mortality to incidence of 0.93), liver cancer is the third most common cause of death from cancer worldwide. The geographical distribution of the mortality rates is similar to that observed for incidence. Worldwide, the major risk factors for liver cancer are infection with hepatitis B and C viruses and consumption of foods contaminated with aflatoxin. Hepatitis B immunization in children has recently been shown to reduce the incidence of liver cancer.⁵

In summary, the incidence rates of many common cancers vary widely by geography. This is due in part to genetic differences, including racial and ethnic differences. It is due also in part to differences in environmental and dietary exposures, factors that can potentially be altered. Therefore, establishment of regional and international databases is critical to improving our understanding of the etiology of cancer and will ultimately assist in the initiation of targeted strategies for global cancer prevention. Furthermore, the monitoring of cancer mortality rates and 5-year cancer-specific survival rates will identify regions where there are inequities of health care, so that access to health care can be facilitated and guidelines for treatment can be established.

CANCER BIOLOGY

Hallmarks of Cancer

Although there are >100 types of cancer, it has been proposed that there are six essential alterations in cell physiology that dictate malignant growth: self-sufficiency of growth signals, insensitivity to growth-inhibitory signals, evasion of apoptosis (programmed cell death), potential for limitless replication, angiogenesis, and invasion and metastasis.⁶ Recently two additional hallmarks have emerged—reprogramming of energy metabolism and evading immune destruction.⁷ These hallmarks of cancer are being pursued as targets for cancer therapy (Figure 10-4).

Cell Proliferation and Transformation

In normal cells, cell growth and proliferation are under strict control. In cancer cells, cells become unresponsive to normal growth controls, which leads to uncontrolled growth and proliferation. Human cells require several genetic changes for neoplastic transformation. Cell type-specific differences also exist for tumorigenic transformation. Abnormally proliferating, transformed cells outgrow normal cells in the culture dish (i.e., in vitro) and commonly display several abnormal characteristics.⁸ These include loss of contact inhibition (i.e., cells continue to proliferate after a confluent monolayer is formed); an altered appearance and poor adherence to other cells or to the substratum; loss of anchorage dependence for growth; immortalization;

Table 10-2

Five-year relative survival rates adjusted to normal life expectancy by year of diagnosis, United States, 1975–2008

CANCER TYPE	RELATIVE 5-YEAR SURVIVAL RATES (%)		
	1975–1977	1987–1989	2002–2008
All cancers	49	56	68
Brain	22	29	35
Breast (female)	75	84	90
Uterine cervix	69	70	69
Colon	51	61	65
Uterine corpus	87	83	83
Esophagus	5	10	19
Hodgkin's disease	72	79	87
Kidney	50	57	72
Larynx	66	66	63
Leukemia	34	43	58
Liver	3	5	16
Lung and bronchus	12	13	17
Melanoma of the skin	82	88	93
Multiple myeloma	25	28	43
Non-Hodgkin's lymphoma	47	51	71
Oral cavity	53	54	65
Ovary	36	38	43
Pancreas	2	4	6
Prostate	68	83	100
Rectum	48	58	68
Stomach	15	20	28
Testis	83	95	96
Thyroid	92	95	98
Urinary bladder	73	79	80

Source: Modified with permission from John Wiley and Sons: Siegel R et al. *Cancer statistics, 2013*. CA: a cancer journal for clinicians. 2013;63:11. © 2013 American Cancer Society, Inc.

and gain of tumorigenicity (i.e., the ability to give rise to tumors when injected into an appropriate host).

Cancer Initiation

Tumorigenesis is proposed to have three steps: initiation, promotion, and progression. Initiating events such as gain of function of genes known as *oncogenes* or loss of function of genes known as *tumor-suppressor genes* may lead a single cell to acquire a distinct growth advantage. Although tumors usually arise from a single cell or clone, it is thought that sometimes not a single cell but rather a large number of cells in a target organ may have undergone the initiating genetic event. Thus, many normal-appearing cells may have an increased malignant potential. This is referred to as a *field effect*. The initiating events are usually genetic and occur as deletions of tumor-suppressor genes or amplification or mutation of oncogenes. Subsequent events can lead to accumulations of additional deleterious mutations in the clone.

Cancer is thought to be a disease of clonal progression as tumors arise from a single cell and accumulate mutations that

confer on the tumor an increasingly aggressive behavior. Most tumors go through a progression from benign lesions to in situ tumors to invasive cancers (e.g., atypical ductal hyperplasia to ductal carcinoma in situ to invasive ductal carcinoma of the breast). Fearon and Vogelstein proposed the model for colorectal tumorigenesis presented in Fig. 10-5.⁹ Colorectal tumors arise from the mutational activation of oncogenes coupled with mutational inactivation of tumor-suppressor genes, the latter being the predominant change.⁹ Mutations in at least four or five genes are required for formation of a malignant tumor, while fewer changes suffice for a benign tumor. Although genetic mutations often occur in a preferred sequence, a tumor's biologic properties are determined by the total accumulation of its genetic changes.

Gene expression is a multistep process that starts from transcription of a gene into messenger ribonucleic acid (mRNA) and then translation of this sequence into the functional protein. There are several controls at each level. In addition to alterations at the genome level (e.g., amplifications of a gene), alterations

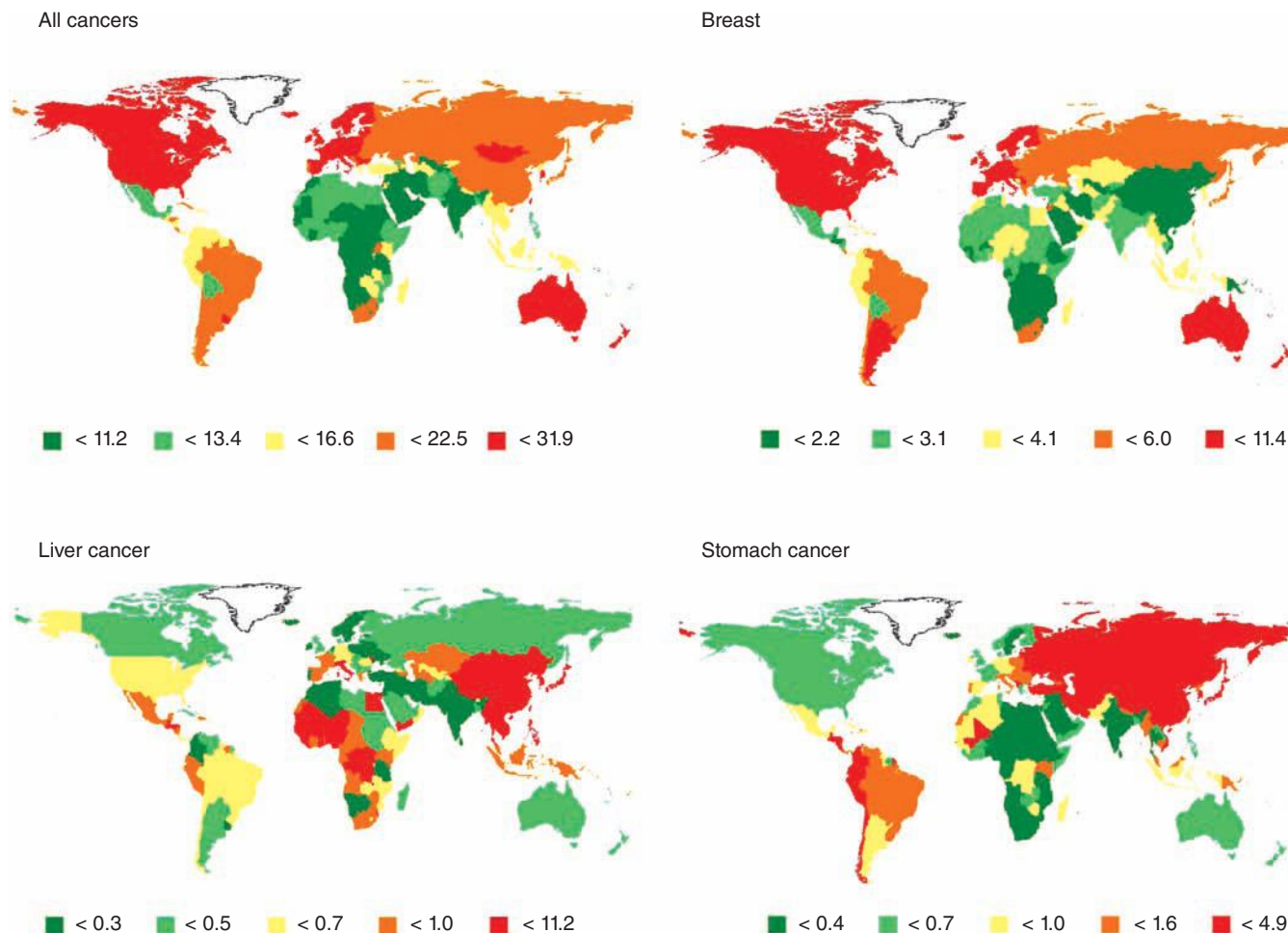


Figure 10-3. Estimated cancer incidence worldwide in 2008. Age-standardized incidence rates per 100,000 for all cancers (upper left), breast cancer (upper right), liver cancer (lower left), and stomach cancer (lower right). (Modified with permission from Ferlay, IARC)⁴

at the transcription level (e.g., methylation of the DNA leading to transcriptional silencing) or at the level of mRNA processing, mRNA stability, mRNA translation, or protein stability, all can alter the levels of critical proteins and thus contribute to tumorigenesis. Alternatively, changes in the genomic sequence can lead to a mutated product with altered function.

Cell-Cycle Dysregulation in Cancer

The proliferative advantage of tumor cells is a result of their ability to bypass quiescence. Cancer cells often show alterations in signal transduction pathways that lead to proliferation in response to external signals. Mutations or alterations in the expression of cell-cycle proteins, growth factors, growth factor receptors, intracellular signal transduction proteins, and nuclear transcription factors all can lead to disturbance of the basic regulatory mechanisms that control the cell cycle, allowing unregulated cell growth and proliferation.

The cell cycle is divided into four phases (Fig. 10-6).¹⁰ During the synthetic or S phase, the cell generates a single copy of its genetic material, whereas in the mitotic or M phase, the cellular components are partitioned between two daughter cells. The G_1 and G_2 phases represent gap phases during which the cells prepare themselves for completion of the S and M phases, respectively. When cells cease proliferation, they exit the cell cycle and enter the quiescent state referred to as G_0 . In human tumor cell-cycle regulators like INK4A, INK4B, and KIP1 are

frequently mutated or altered in expression. These alterations underscore the importance of cell-cycle regulation in the prevention of human cancers.

Oncogenes

Normal cellular genes that contribute to cancer when abnormal are called *oncogenes*. The normal counterpart of such a gene is referred to as a *proto-oncogene*. Oncogenes are usually designated by three-letter abbreviations, such as *myc* or *ras*. Oncogenes are further designated by the prefix “v-” for virus or “c-” for cell or chromosome, corresponding to the origin of the oncogene when it was first detected. Proto-oncogenes can be activated (show increased activity) or overexpressed (expressed at increased protein levels) by translocation (e.g., *abl*), promoter insertion (e.g., *c-myc*), mutation (e.g., *ras*), or amplification (e.g., *HER2/neu*). More than 100 oncogenes have been identified.

Oncogenes may be growth factors (e.g., platelet-derived growth factor), growth factor receptors (e.g., *HER2*), intracellular signal transduction molecules (e.g., *ras*), nuclear transcription factors (e.g., *c-myc*), or other molecules involved in the regulation of cell growth and proliferation. Growth factors are ubiquitous proteins that are produced and secreted by cells locally and that stimulate cell proliferation by binding specific cell-surface receptors on the same cells (autocrine stimulation) or on neighboring cells (paracrine stimulation). Persistent overexpression

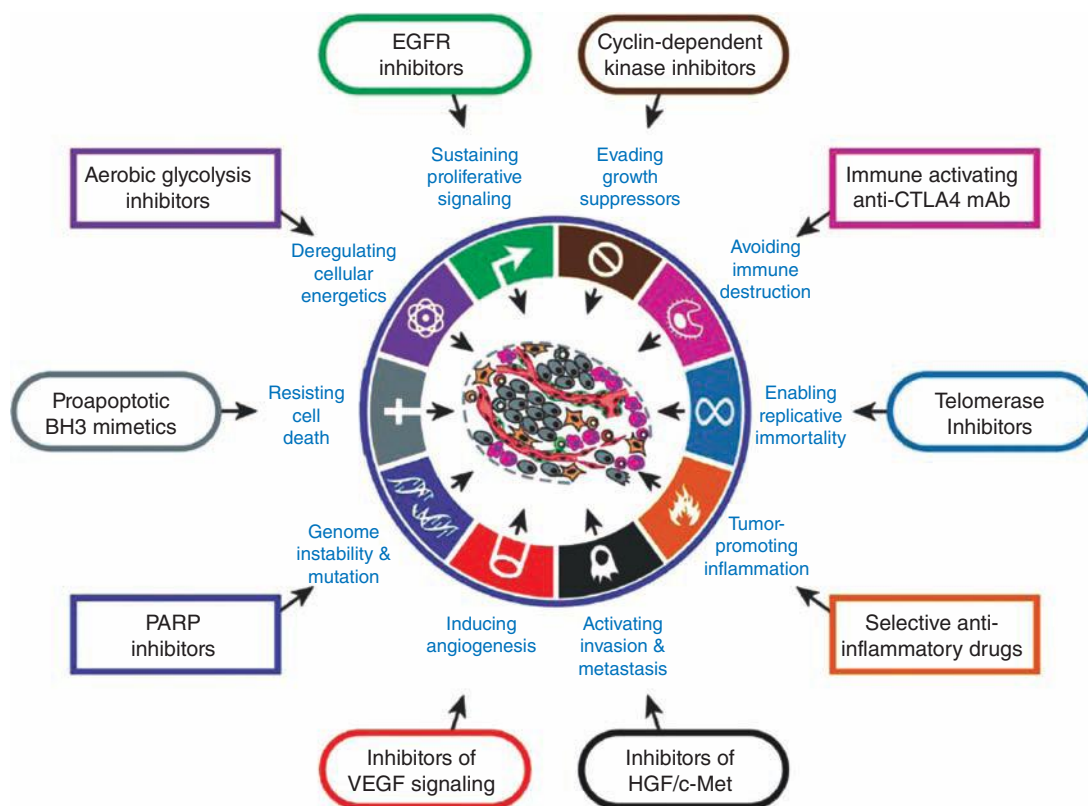


Figure 10-4. Hallmarks of cancer and their therapeutic implications. Drugs that interfere with each of the acquired capabilities necessary for tumor growth and progression are in clinical trials and in some cases approved for clinical use in treating forms of human cancer. The drugs listed are illustrative examples. (Modified with permission from Hanahan et al. Copyright Elsevier.)⁷

of growth factors can lead to uncontrolled autostimulation and neoplastic transformation. Alternatively, growth factor receptors can be aberrantly activated (turned on) through mutations or overexpressed (continually presenting cells with growth-stimulatory signals, even in the absence of growth factors), which leads cells to respond as if growth factor levels are altered. The growth-stimulating effect of growth factors and other mitogens is mediated through postreceptor signal transduction molecules.

These molecules mediate the passage of growth signals from the outside to the inside of the cell and then to the cell nucleus, initiating the cell cycle and DNA transcription. Aberrant activation or expression of cell-signaling molecules, cell-cycle molecules, or transcription factors may play an important role in neoplastic transformation. Protein tyrosine kinases account for a large portion of known oncogenes. One of the best-studied oncogenes, *HER2* is discussed as an example later.

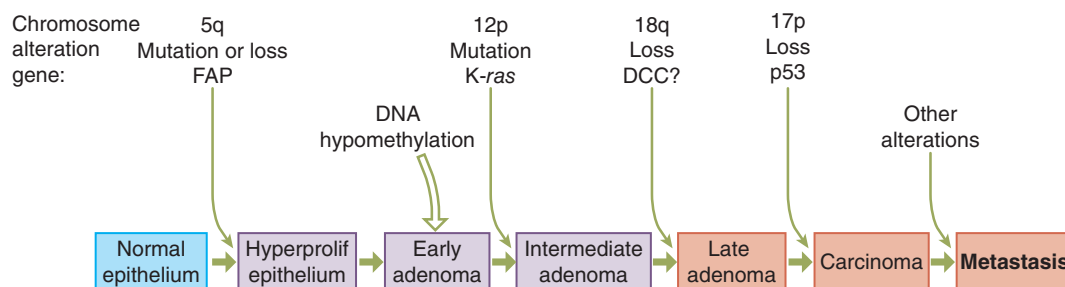


Figure 10-5. A genetic model for colorectal tumorigenesis. Tumorigenesis proceeds through a series of genetic alterations involving oncogenes and tumor-suppressor genes. In general, the three stages of adenomas represent tumors of increasing size, dysplasia, and villous content. Individuals with familial adenomatous polyposis (FAP) inherit a mutation on chromosome arm 5q. In tumors arising in individuals without polyposis, the same region may be lost or mutated at a relatively early stage of tumorigenesis. A *ras* gene mutation (usually *K-ras*) occurs in one cell of a pre-existing small adenoma which, through clonal expansion, produces a larger and more dysplastic tumor. The chromosome arms most frequently deleted include 5q, 17p, and 18q. Allelic deletions of chromosome arms 17p and 18q usually occur at a later stage of tumorigenesis than do deletions of chromosome arm 5q or *ras* gene mutations. The order of these changes varies, however, and accumulation of these changes, rather than their order of appearance, seems most important. Tumors continue to progress once carcinomas have formed, and the accumulated chromosomal alterations correlate with the ability of the carcinomas to metastasize and cause death. DCC = deleted in colorectal cancer gene. (Modified with permission from Fearon et al. Copyright Elsevier.)⁹

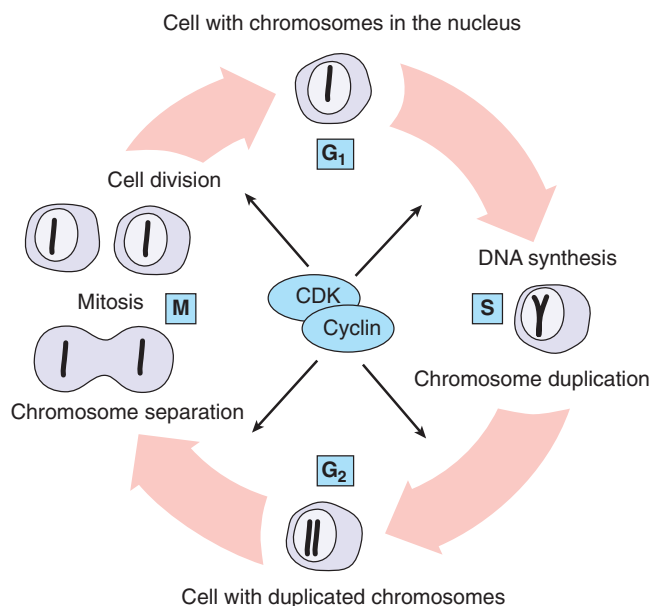


Figure 10-6. Schematic representation of the phases of the cell cycle. Mitogenic growth factors can drive a quiescent cell from G₀ into the cell cycle. Once the cell cycle passes beyond the restriction point, mitogens are no longer required for progression into and through S phase. The DNA is replicated in S phase, and the chromosomes are condensed and segregated in mitosis. In early G₁ phase, certain signals can drive a cell to exit the cell cycle and enter a quiescent phase. Cell-cycle checkpoints have been identified in G₁, S, G₂, and M phases. CDK = cyclin-dependent kinase. (Adapted from Kastan *et al*)¹⁰

HER2, also known as *neu* or *c-erbB-2*, is a member of the epidermal growth factor receptor (EGFR) family and is one of the best-characterized tyrosine kinases. Unlike other receptor tyrosine kinases, *HER2/neu* does not have a direct soluble ligand. It plays a key role in signaling, however, because it is the preferred partner in heterodimer formation with all the other EGFR family members (*EGFR/c-erbB-1*, *HER2/c-erbB-3*, and *HER3/c-erbB-4*), which bind at least 30 ligands, including epidermal growth factor (EGF), transforming growth factor α (TGF α), heparin-binding EGF-like growth factor, amphiregulin, and heregulin.¹¹ Heterodimerization with *HER2* potentiates recycling of receptors rather than degradation, enhances signal potency and duration, increases affinity for ligands, and increases catalytic activity.¹¹

HER2 can interact with different members of the HER family and activate mitogenic and antiapoptotic pathways (Fig. 10-7). The specificity and potency of the intracellular signals are affected by the identity of the ligand, the composition of the receptors, and the phosphotyrosine-binding proteins associated with the erbB molecules. The Ras- and Shc-activated mitogen-activated protein kinase (MAPK) pathway is a target of all erbB ligands, which increase the transcriptional activity of early response genes such as *c-myc*, *c-fos*, and *c-jun*.¹² MAPK-independent pathways such as the phosphoinositide-3 kinase (PI3K) pathway also are activated by most erbB dimers, although the potency and kinetics of activation may differ. Stimulation of the PI3K pathway through *HER2* signaling also can lead to activation of survival molecule Akt, which suppresses apoptosis through multiple mechanisms. The critical role of *HER2* in cancer biology has been leveraged for therapeutics, leading to several *HER2*-targeted drugs with different mechanism of action

approved by the Food and Drug Administration (FDA): monoclonal antibodies trastuzumab and pertuzumab, small molecule inhibitor lapatinib, and antibody-drug conjugate ado-trastuzumab emtansine.

The mutant rat *neu* gene was first recognized as an oncogene in neuroblastomas from carcinogen-treated rats.¹³ The *HER2* gene is frequently amplified and the protein overexpressed in many cancers, including breast, ovarian, lung, gastric, and oral cancers. Overexpression of *HER2* results in ligand-independent activation of *HER2* kinase, which leads to mitogenic signaling. *HER2* overexpression is associated with increased cell proliferation and anchorage-independent growth as well as resistance to proapoptotic stimuli. Further, overexpression of *HER2* increases cell migration and upregulates the activities of matrix metalloproteinases (MMPs) and in vitro invasiveness. In animal models, *HER2* increases tumorigenicity, angiogenesis, and metastasis. These results all suggest that *HER2* plays a key role in cancer biology. More recently *HER2* mutations have also been reported in human cancer. *HER2* mutations have been detected in 2% to 4% of nonsmall cell lung cancer.¹⁴⁻¹⁷ In frame insertions within exon 20 has been the most commonly reported mutation. *HER2* mutations are more common in nonsmokers and are nonoverlapping with other oncogenic mutations in lung cancer (e.g., EGFR and Ras). Data from 8 breast cancer genome-sequencing projects identified 25 patients with *HER2* somatic mutations in cancers lacking *HER2* gene amplification.¹⁸ Seven of 13 mutations were functionally characterized and found to be activating mutations. All of these mutations were sensitive to the irreversible kinase inhibitor, neratinib. A prospective, multi-institutional clinical trial has been launched to screen patients with stage IV breast cancer for *HER2* somatic mutations and determine the clinical outcome of treating them with *HER2*-targeted therapy.

Alterations in Apoptosis in Cancer Cells

Apoptosis is a genetically regulated program to dispose of cells. Cancer cells must avoid apoptosis if tumors are to arise. The growth of a tumor mass is dependent not only on an increase in proliferation of tumor cells but also on a decrease in their apoptotic rate. Apoptosis is distinguished from necrosis because it leads to several characteristic changes. In early apoptosis, the changes in membrane composition lead to extracellular exposure of phosphatidylserine residues, which avidly bind annexin, a characteristic that is used to discriminate apoptotic cells in laboratory studies. Late in apoptosis there are characteristic changes in nuclear morphology, such as chromatin condensation, nuclear fragmentation, and DNA laddering, as well as membrane blebbing. Apoptotic cells are then engulfed and degraded by phagocytic cells. The effectors of apoptosis are a family of proteases called *caspases* (cysteine-dependent and aspartate-directed proteases). The initiator caspases (e.g., 8, 9, and 10), which are upstream, cleave the downstream executioner caspases (e.g., 3, 6, and 7) that carry out the destructive functions of apoptosis.

Two principal molecular pathways signal apoptosis by cleaving the initiator caspases with the potential for crosstalk: the mitochondrial pathway and the death receptor pathway. In the mitochondrial (or intrinsic) pathway, death results from the release of cytochrome c from the mitochondria. Cytochrome c, procaspase 9, and apoptotic protease activating factor 1 (Apaf-1) form an enzyme complex, referred to as the *apoptosome*, that activates the effector caspases. In addition to these proteins,

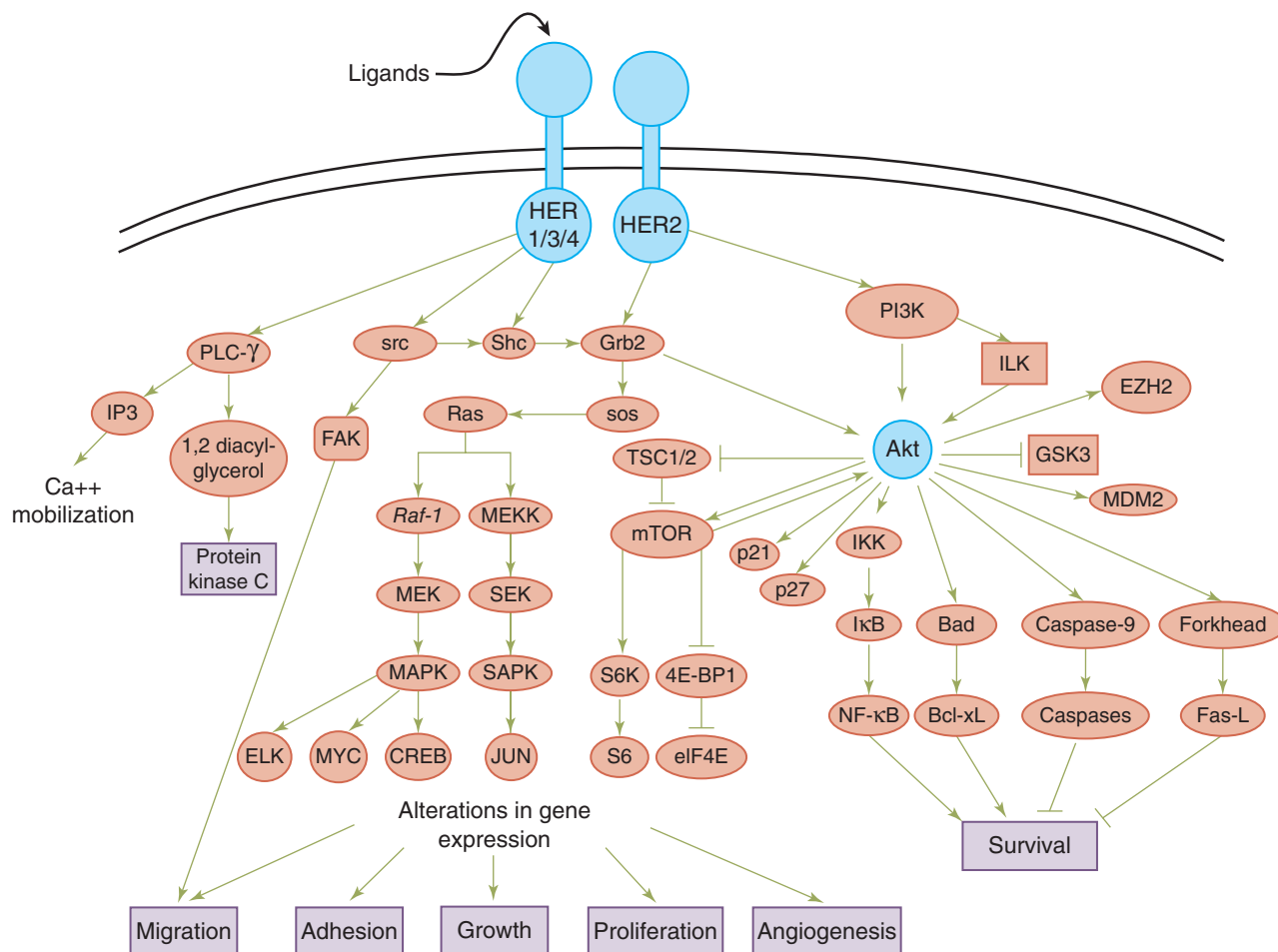


Figure 10-7. The HER2 signaling pathway. HER2 can interact with different members of the HER family and activate mitogenic and antiapoptotic pathways. 4E-BP1 = eIF4E binding protein 1; CREB = cyclic adenosine monophosphate element binding; eIF4E = eukaryotic initiation factor 4E; EZH = enhancer of zeste homolog; FAK = focal adhesion kinase; Fas-L = Fas ligand; GSK3 = glycogen synthase kinase-3; HER = human epidermal growth receptor; IKK = I κ B kinase; ILK = integrin-linked kinase; IP3 = inositol triphosphate; I κ B = inhibitor of NF- κ B; MAPK = mitogen-activated protein kinase; MDM2 = mouse double minute 2 homologue; MEK = mitogen-activated protein/extracellular signal regulated kinase kinase; MEKK = MEK kinase; mTOR = mammalian target of rapamycin; NF- κ B = nuclear factor κ B; PI3K = phosphoinositide-3 kinase; PLC- γ = phospholipase C γ ; SAPK = stress-activated protein kinase; SEK = SAPK/extracellular signal regulated kinase kinase; TSC = tuberous sclerosis complex. (Modified with permission from Meric-Bernstam et al.)¹⁷¹

the mitochondria contain other proapoptotic proteins such as second mitochondria-derived activator of caspase/direct inhibitor of apoptosis-binding protein with low pI (Smac/DIABLO). The mitochondrial pathway can be stimulated by many factors, including DNA damage, reactive oxygen species, or the withdrawal of survival factors. The permeability of the mitochondrial membrane determines whether the apoptotic pathway will proceed. The Bcl-2 family of regulatory proteins includes both proapoptotic proteins (e.g., Bax, BAD, and Bak) and antiapoptotic proteins (e.g., Bcl-2 and Bcl-xL). The activity of the Bcl-2 proteins is centered on the mitochondria, where they regulate membrane permeability. Growth factors promote survival signaling through the PI3K/Akt pathway, which phosphorylates and inactivates proapoptotic BAD. In contrast, growth factor withdrawal may promote apoptosis through signaling by unphosphorylated BAD. The heat shock proteins, including Hsp70 and Hsp27, are also involved in inhibition of downstream apoptotic pathways by blocking formation of the apoptosome complex and inhibiting release of cytochrome c from the mitochondria.¹⁹

The second principal apoptotic pathway is the death receptor pathway, sometimes referred to as the *extrinsic pathway*.

Cell-surface death receptors include Fas/APO1/CD95, tumor necrosis factor receptor 1, and KILL-ER/DR5, which bind their ligands Fas-L, tumor necrosis factor (TNF), and TNF-related apoptosis-inducing ligand (TRAIL), respectively. When the receptors are bound by their ligands, they form a death-inducing signaling complex (DISC). At the DISC, procaspase 8 and procaspase 10 are cleaved, yielding active initiator caspases.²⁰ The death receptor pathway may be regulated at the cell surface by the expression of “decoy” receptors for Fas (DcR3) and TRAIL (TRID and TRUND). The decoy receptors are closely related to the death receptors but lack a functional death domain; therefore, they bind death ligands but do not transmit a death signal. Another regulatory group is the FADD-like interleukin-1 protease-inhibitory proteins (FLIPs). FLIPs have homology to caspase 8; they bind to the DISC and inhibit the activation of caspase 8. Finally, inhibitors of apoptosis proteins (IAPs) block caspase 3 activation and have the ability to regulate both the death receptor and the mitochondrial pathway.

In human cancers, aberrations in the apoptotic program include increased expression of Fas and TRAIL decoy receptors; increased expression of antiapoptotic Bcl-2; increased expression

of the IAP-related protein survivin; increased expression of c-FLIP; mutations or downregulation of proapoptotic Bax, caspase 8, APAF1, XAF1, and death receptors CD95, TRAIL-R1, and TRAIL-R2; alterations of the p53 pathway; overexpression of growth factors and growth factor receptors; and activation of the PI3K/Akt survival pathway.²⁰

Autophagy in Cancer Cells

Autophagy (self-eating) is a major cellular pathway for protein and organelle turnover. This process helps maintain a balance between anabolism and catabolism for normal cell growth and development. Inability to activate autophagy in response to nutrient deprivation, or constitutive activation of autophagy in response to stress, can lead to cell death; thus autophagy is sometimes referred to as a second form of programmed cell death. Autophagy plays an essential role during starvation, cellular differentiation, cell death, and aging. Autophagy is also involved in the elimination of cancer cells by triggering a nonapoptotic cell death program, which suggests a negative role in tumor development. Mouse models that are heterozygotes for the beclin 1 gene, an important gene for autophagy, have altered autophagic response and show a high incidence of spontaneous tumors, which establishes a role for autophagy in tumor suppression.²¹ This also suggests that mutations in other genes operating in this pathway may contribute to tumor formation through deregulation of autophagy. However, autophagy also acts as a stress response mechanism to protect cancer cells from low nutrient supply or therapeutic insults. Studies on the molecular determinants of autophagy are ongoing to determine whether autophagy can be modulated for therapeutic purposes.

Cancer Invasion

A feature of malignant cells is their ability to invade the surrounding normal tissue. Tumors in which the malignant cells appear to lie exclusively above the basement membrane are referred to as *in situ cancer*, whereas tumors in which the malignant cells are demonstrated to breach the basement membrane, penetrating into surrounding stroma, are termed *invasive cancer*. The ability to invade involves changes in adhesion, initiation of motility, and proteolysis of the extracellular matrix (ECM).

Cell-to-cell adhesion in normal cells involves interactions between cell-surface proteins. Calcium adhesion molecules of the cadherin family (E-cadherin, P-cadherin, and N-cadherin) are thought to enhance the cells' ability to bind to one another and suppress invasion. Migration occurs when cancer cells penetrate and attach to the basal matrix of the tissue being invaded; this allows the cancer cell to pull itself forward within the tissue. Attachment to glycoproteins of the ECM such as fibronectin, laminin, and collagen is mediated by tumor cell integrin receptors. Integrins are a family of glycoproteins that form heterodimeric receptors for ECM molecules. The integrins can form at least 25 distinct pairings of their α and β subunits, and each pairing is specific for a unique set of ligands. In addition to regulating cell adhesion to the ECM, integrins relay molecular signals regarding the cellular environment that influence shape, survival, proliferation, gene transcription, and migration.

Factors that are thought to play a role in cancer cell motility include autocrine motility factor, autotaxin, scatter factor (also known as *hepatocyte growth factor*), TGF α , EGF, and insulin-like growth factors.

Serine, cysteine, and aspartic proteinases and MMPs have all been implicated in cancer invasion. Urokinase and tissue

plasminogen activators (uPA and tPA) are serine proteases that convert plasminogen into plasmin. Plasmin, in return, can degrade several ECM components. Plasmin also may activate MMPs. uPA has been more closely correlated with tissue invasion and metastasis than tPA. Plasminogen activator inhibitors 1 and 2 (PAI-1 and PAI-2) are produced in tissues and counteract the activity of plasminogen activators.

MMPs comprise a family of metal-dependent endopeptidases. Upon activation, MMPs degrade a variety of ECM components. Although MMPs often are referred to by their common names, which reflect the ECM component for which they have specificity, a sequential numbering system has been adopted for standardization. For example, collagenase-1 is now referred to as *MMP-1*. The MMPs are further classified as secreted and membrane-type MMPs. Most of the MMPs are synthesized as inactive zymogens (pro-MMP) and are activated by proteolytic removal of the propeptide domain outside the cell by other active MMPs or serine proteinases.

MMPs are upregulated in almost every type of cancer. Some of the MMPs are expressed by cancer cells, whereas others are expressed by the tumor stromal cells. Experimental models have demonstrated that MMPs promote cancer progression by increasing cancer cell growth, migration, invasion, angiogenesis, and metastasis. MMPs exert these effects by cleaving not only structural components of the ECM but also growth factor-binding proteins, growth factor precursors, cell adhesion molecules, and other proteinases. The activity of MMPs is regulated by their endogenous inhibitors and tissue inhibitors of MMPs (TIMP-1, TIMP-2, TIMP-3, and TIMP-4).

Angiogenesis

Angiogenesis is the establishment of new blood vessels from a pre-existing vascular bed. This neovascularization is essential for tumor growth and metastasis. Tumors develop an angiogenic phenotype as a result of accumulated genetic alterations and in response to local selection pressures such as hypoxia. Many of the common oncogenes and tumor-suppressor genes have been shown to play a role in inducing angiogenesis.

In response to the angiogenic switch, pericytes retract and the endothelium secretes several growth factors such as basic fibroblast growth factor, platelet-derived growth factor (PDGF), and insulin-like growth factor. The basement membrane and stroma around the capillary are proteolytically degraded, a process that is mediated in most part by uPA. The endothelium then migrates through the degraded matrix, initially as a solid cord and later forming lumina. Finally, sprouting tips anastomose to form a vascular network surrounded by a basement membrane.

Angiogenesis is mediated by factors produced by various cells, including tumor cells, endothelial cells, stromal cells, and inflammatory cells. The first proangiogenic factor was identified by Folkman and colleagues in 1971.²² Since then, several other factors have been shown to be proangiogenic or antiangiogenic. Of the angiogenic stimulators, the best studied are the vascular endothelial growth factors (VEGFs). The VEGF family consists of six growth factors (VEGF-A, VEGF-B, VEGF-C, VEGF-D, VEGF-E, and placental growth factor) and three receptors (VEGFR1 or Flt-1, VEGFR2 or KDR/FLK-1, and VEGFR3 or Flt-4).²³ Neuropilin 1 and 2 also may act as receptors for VEGF.²⁴ VEGF is induced by hypoxia and by different growth factors and cytokines, including EGF, PDGF, TNF- α , TGF β , and interleukin-1 β . VEGF has various functions, including increasing vascular permeability, inducing endothelial cell

proliferation and tube formation, and inducing endothelial cell synthesis of proteolytic enzymes such as uPA, PAI-1, urokinase plasminogen activator receptor, and MMP-1. Furthermore, VEGF may mediate blood flow by its effects on the vasodilator nitric oxide and act as an endothelial survival factor, thus protecting the integrity of the vasculature. The proliferation of new lymphatic vessels, lymphangiogenesis, is also thought to be controlled by the VEGF family. Signaling in lymphatic cells is thought to be modulated by VEGFR3.²⁵ Experimental studies with VEGF-C and VEGF-D have shown that they can induce tumor lymphangiogenesis and direct metastasis via the lymphatic vessels and lymph nodes.^{25, 26}

PDGFs A, B, C, and D also play important roles in angiogenesis. PDGFs cannot only enhance endothelial cell proliferation directly but also upregulate VEGF expression in vascular smooth muscle cells, promoting endothelial cell survival via a paracrine effect.²³ The angiopoietins angiopoietin-1 and angiopoietin-2 (Ang-1 and Ang-2), in return, are thought to regulate blood vessel maturation. Ang-1 and Ang-2 both bind angiopoietin-1 receptor (also known as tyrosine-protein kinase receptor TIE-2), but only the binding of Ang-1 activates signal transduction; thus Ang-2 is an Ang-1 antagonist. Ang-1, via the Tie-2 receptor, induces remodeling and stabilization of blood vessels. Upregulation of Ang-2 by hypoxic induction of VEGF inhibits Ang-1-induced Tie-2 signaling, which results in destabilization of vessels and makes endothelial cells responsive to angiogenic

signals, thus promoting angiogenesis in the presence of VEGF. Therefore the balance between these factors determines the angiogenic capacity of a tumor.

Tumor angiogenesis is regulated by several factors in a coordinated fashion. In addition to upregulation of proangiogenic molecules, angiogenesis also can be encouraged by suppression of naturally occurring inhibitors. Such inhibitors of angiogenesis include thrombospondin 1 and angiostatin. Angiogenesis is a prerequisite not only for primary tumor growth but also for metastasis. Angiogenesis in the primary tumor, as determined by microvessel density, has been demonstrated to be an independent predictor of distant metastatic disease and survival in several cancers. Expression of angiogenic factors such as VEGFs has had prognostic value in many studies. These findings further emphasize the importance of angiogenesis in cancer biology.

Metastasis

Metastases arise from the spread of cancer cells from the primary site and the formation of new tumors in distant sites. The metastatic process consists of a series of steps that need to be completed successfully (Fig. 10-8).²⁷ First, the primary cancer must develop access to the circulation through either the blood circulatory system or the lymphatic system. After the cancer cells are shed into the circulation, they must survive. Next, the circulating cells lodge in a new organ and extravasate into the

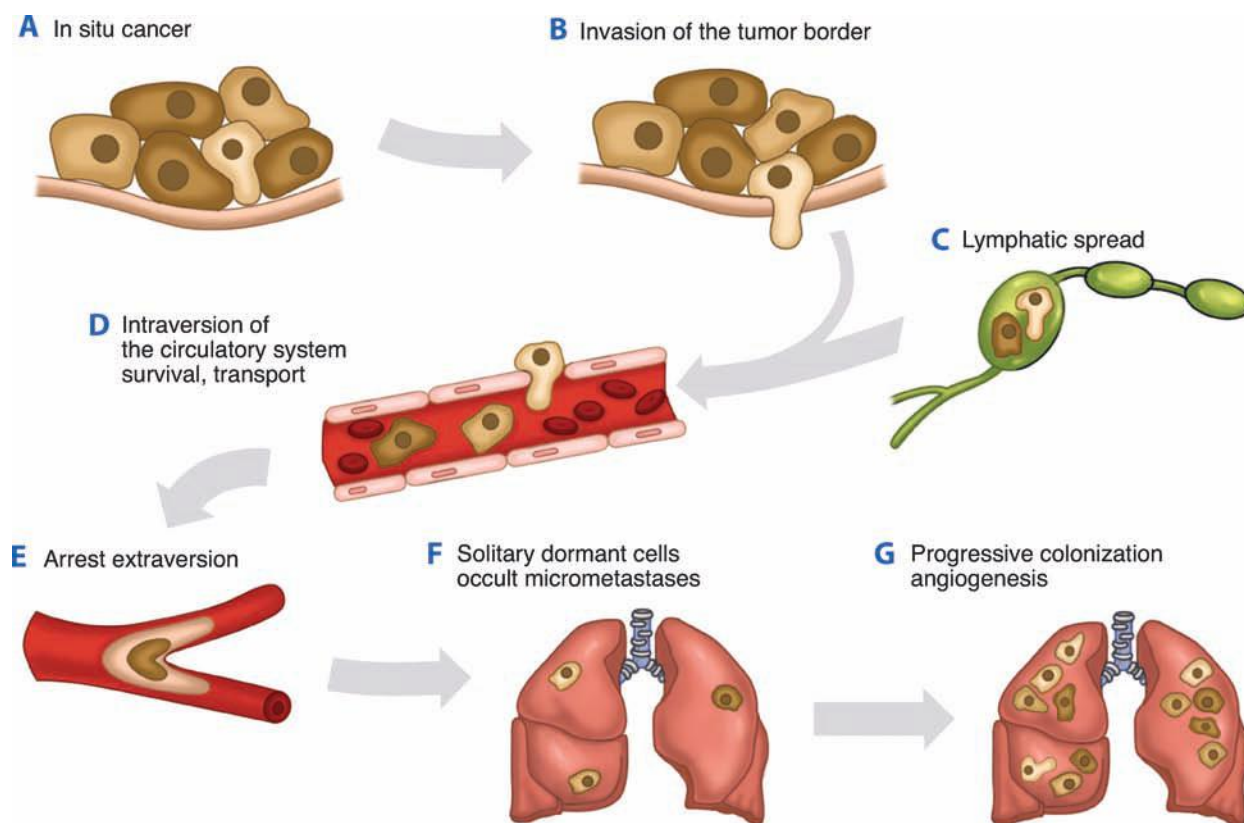


Figure 10-8. A schematic representation of the metastatic process. **A.** The metastatic process begins with an in situ cancer surrounded by an intact basement membrane. **B.** Invasion requires reversible changes in cell-cell and cell-extracellular matrix adherence, destruction of proteins in the matrix and stroma, and motility. **C.** Metastasizing cells can enter the circulation via the lymphatics. **D.** They can also directly enter the circulation. **E.** Intravascular survival of the tumor cells and extravasation of the circulatory system follow. **F.** Metastatic single cells can colonize sites and remain dormant for years as occult micrometastases. **G.** Subsequent progression and neovascularization leads to clinically detectable metastases and progressively growing, angiogenic metastases. (Adapted by permission from Macmillan Publishers Ltd. Steeg PS. *Metastasis suppressors alter the signal transduction of cancer cells.* Nat Rev Cancer. 2003;3:55. Copyright © 2003.)²⁷

new tissue. Next, the cells need to initiate growth in the new tissue and eventually establish vascularization to sustain the new tumor. Overall, metastasis is an inefficient process, although the initial steps of hematogenous metastasis (the arrest of tumor cells in the organ and extravasation) are believed to be performed efficiently. Only a small subset of cancer cells is then able to initiate micrometastases, and an even smaller portion goes on to grow into macrometastases.

Metastases can sometimes arise several years after the treatment of primary tumors. For example, although most breast cancer recurrences occur within the first 10 years after the initial treatment and recurrences are rare after 20 years, breast cancer recurrences have been reported decades after the original tumor. This phenomenon is referred to as *dormancy*, and it remains one of the biggest challenges in cancer biology. Persistence of solitary cancer cells in a secondary site such as the liver or bone marrow is one possible contributor to dormancy.²⁸ Another explanation of dormancy is that cells remain viable in a quiescent state and then become reactivated by a physiologically perturbing event. Interestingly, primary tumor removal has been proposed to be a potentially perturbing factor.²⁹ An alternate explanation is that cells establish preangiogenic metastases in which they continue to proliferate but that the proliferative rate is balanced by the apoptotic rate. Therefore, when these small metastases acquire the ability to become vascularized, substantial tumor growth can be achieved at the metastatic site, leading to clinical detection.

Several types of tumors metastasize in an organ-specific pattern. One explanation for this is mechanical and is based on the different circulatory drainage patterns of the tumors. When different tumor types and their preferred metastasis sites were compared, 66% of organ-specific metastases were explained on the basis of blood flow alone. The other explanation for preferential metastasis is what is referred to as the “*seed and soil*” theory, the dependence of the seed (the cancer cell) on the soil (the secondary organ). According to this theory, once cells have reached a secondary organ, their growth efficiency in that organ is based on the compatibility of the cancer cell’s biology with its new microenvironment. For example, breast cancer cells may grow more efficiently in bone than in some other organs because of favorable molecular interactions that occur in the bone microenvironment. The ability of cancer cells to grow in a specific site likely depends on features inherent to the cancer cell, features inherent to the organ, and the interplay between the cancer cell and its microenvironment.³⁰

Many of the oncogenes discovered to date, such as *HER2* and *ras*, are thought to potentiate not only malignant transformation but also one or more of the steps required in the metastatic process. Experimental models have suggested a role for several molecules, including RhoC, osteopontin and interleukin-11, and Twist, in tumor metastasis. Metastasis also may involve the loss of metastasis-suppressor genes. Laboratory work involving cancer cell lines that have been selected to have a higher metastatic potential have led to the realization that these more highly metastatic cells have a different gene expression profile than their less metastatic parental counterparts. This in turn has led to the currently held belief that the ability of a primary tumor to metastasize may be predictable by analysis of its gene expression profile. Indeed, several studies have recently focused on identifying a gene expression profile or a molecular signature that is associated with metastasis. It has been shown that such a gene expression profile can be used to predict the probability that the

patient will remain free of distant metastasis.³¹ This suggests that the metastatic potential of a tumor is already predetermined by the genetic alterations that the cancer cells acquire early in tumorigenesis. Notably, this hypothesis differs from the multistep tumorigenesis theory in that the ability to metastasize is considered an inherent quality of the tumor from the beginning. It is assumed that metastasis develops not from a few rare cells in the primary tumor that acquire the ability to metastasize but that all cells in tumors with such molecular signatures develop the ability to metastasize. The reality probably lies in between since some early genetic changes detectable in the entire tumor can give tumors an advantage in the metastatic process, whereas additional genetic changes can give a clone of cells additional advantages, thus allowing them to succeed in metastasis.

Epithelial-Mesenchymal Transition

A regulatory program referred to as epithelial-mesenchymal transition (EMT) is a fundamental event in morphogenesis. During EMT epithelial cells are converted to migratory and invasive cells.³² EMT, has also been implicated as the mechanism through which epithelial cells acquire the ability to migrate, invade, resist apoptosis and metastasize. EMT is a developmental process, and a set of pleiotropically acting transcriptional factors, including Snail, Twist, Slug, and Zeb1/2 orchestrate EMT. Several of these transcription factors can directly repress E-cadherin gene expression, depriving cancer cells of this key suppressor of motility and invasiveness. It has been proposed that the process of invasion and metastases requires significant plasticity, suggesting that EMT is required for invasion, intravasation and extravasation, and suppression of EMT regulators (and consequently EMT reversion, or MET) is required for metastatic outgrowth.³³⁻³⁵

Cancer Stem Cells

Stem cells are cells that have the ability to perpetuate themselves through self-renewal and to generate mature cells of a particular tissue through differentiation.³⁶ It has recently been proposed that stem cells themselves may be the target of transformation. It was first documented for leukemia and multiple myeloma that only a small subset of cancer cells is capable of extensive proliferation. It has subsequently also been shown for many solid cancers that only a small proportion of cells is clonogenic in culture and in vivo. In leukemia and multiple myeloma only a small subset of cancer cells is capable of extensive proliferation. Similarly, in many solid tumor types only a small proportion of cells is clonogenic in culture and in vivo. If indeed tumor growth and metastasis are driven by a small population of cancer stem cells, this may alter our current approaches to cancer therapy. Currently available drugs can shrink metastatic tumors but often cannot eradicate them. The failure of these treatments usually is attributed to the acquisition of drug resistance by the cancer cells; however, the cancer stem cell hypothesis raises the possibility that existing therapies may simply fail to kill cancer stem cells effectively. Therapeutic approaches targeting stem cells specifically are under study.

CANCER ETIOLOGY

Cancer Genomics

One widely held opinion is that cancer is a genetic disease that arises from an accumulation of genomic alterations that leads to the selection of cells with increasingly aggressive behavior. These alterations may lead either to a gain of function by oncogenes

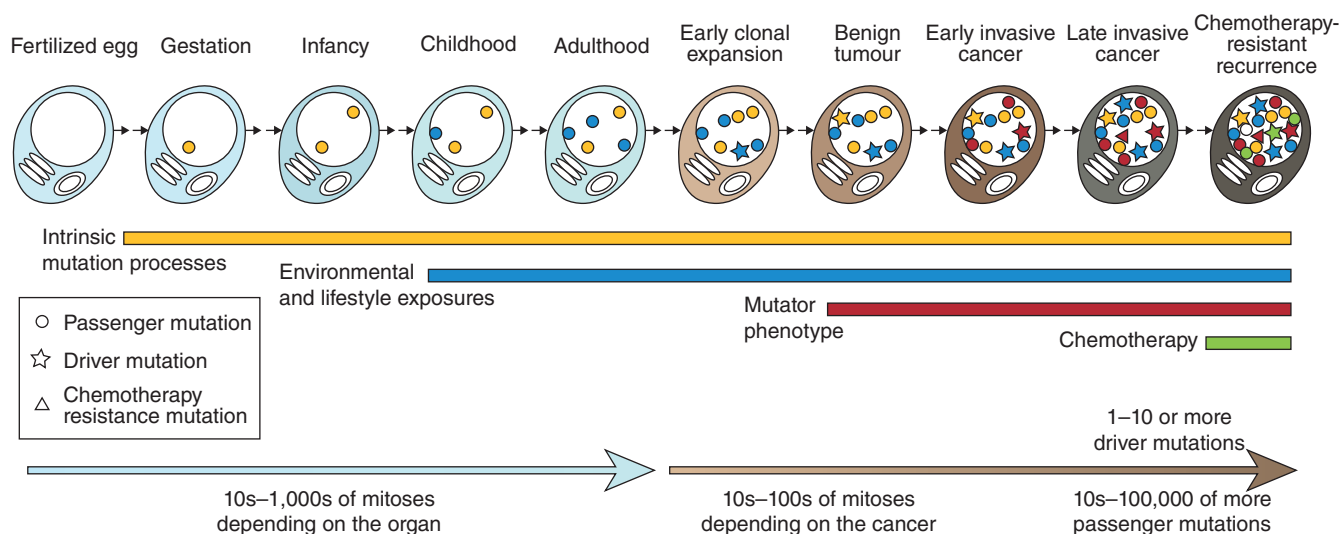


Figure 10-9. Accumulation of somatic mutations acquired by the cancer cell. Mutations may be acquired while the cell lineage is phenotypically normal, reflecting intrinsic mutations acquired during normal cell division as well as the effects of exogenous mutagens. Other processes such as example DNA repair defects may contribute to the mutational burden. Passenger mutations do not have any effect on the cancer cell, but driver mutations cause clonal expansion. Relapse after chemotherapy can be associated with resistance mutations that may predate the initiation of treatment. (Adapted by permission from Macmillan Publishers Ltd. Stratton MR, Campbell PJ, Futreal PA. *The cancer genome*. Nature. 2009;458:719. Copyright © 2009.)³⁷

or to a loss of function by tumor-suppressor genes. These acquired gene alterations are termed somatic mutations to distinguish them from germline mutations that are inherited from parents and transmitted to offspring. Somatic mutations in a cancer genome may consist of several classes of DNA sequence changes. These include substitutions of one base by another; insertions or deletions of small or large segments of DNA; rearrangements, in which the DNA sequence has been broken and then rejoined to another DNA segment; copy number losses that may result in complete absence of a DNA sequence and copy number gains from the two copies present in the normal diploid genome.

Somatic mutations in a cancer cell genome have accumulated over the lifetime of the patient (Fig. 10-9).³⁷ DNA in normal cells is continuously damaged by internal and external mutagens. Most of this damage is repaired; however, a small fraction may remain as fixed mutations. Mutation rates increase in the presence of substantial exogenous mutagenic exposures, such as tobacco carcinogens or various forms of radiation, including ultraviolet light. These exposures are associated with increased rates of lung and skin cancer, respectively, and somatic mutations within such cancers often exhibit the distinctive mutational signatures known to be associated with the mutagen.³⁸ The rates of somatic mutations are also increased in several rare inherited diseases, such as Fanconi anemia, ataxia telangiectasia, and xeroderma pigmentosum, which are associated with increased risks of cancer.^{39, 40} The rest of the somatic mutations in a cancer cell have been acquired after the cancer cell already shows phenotypic evidence of neoplastic change. Whether the somatic mutation rate is always higher during this part of the lineage is controversial. This is clearly the case for some cancers. For instance, colorectal and endometrial cancers with defective DNA mismatch repair due to abnormalities in genes such as *MLH1* and *MSH2*, exhibit increased rates of single nucleotide changes and small insertions/deletions at polynucleotide tract.⁴¹ These tumor types are often referred to as “mutator phenotypes.”

To date about 300 genes that have been reported to be mutated and causally implicated in cancer development.⁴² Ninety percent of cancer genes show somatic mutations in cancer, 20% show germline mutations, and 10% show both. The most common class of genomic alterations among the known cancer genes is a chromosomal translocation that creates a chimeric gene. Many more cancer genes have been found in leukemias, lymphomas, and sarcomas than in other types of cancer; and these genes are usually altered by chromosomal translocation. The most common cancer genes are protein kinases. Several domains that are involved in DNA binding and transcriptional regulation are also common in proteins encoded by cancer genes. Somatic mutations in a cancer genome may be classified according to its consequences for cancer development. “Driver” mutations confer a growth advantage to the cells carrying them and have been positively selected during the evolution of the cancer. The remainder of mutations are “bystanders” or “passengers” that do not confer growth advantage. It is likely that most somatic mutations are passenger mutations. Each tumor may have dozens to hundreds of genomic alterations, making it critical to determine which alterations are indeed drivers, and potentially better therapeutic targets.

There are several ongoing large scale studies to characterize and catalogue genomic alterations in different cancer types, including the Cancer Genome Project at the Sanger Institute, United Kingdom, and The Cancer Genome Atlas project (TCGA). There are also increasing number of publically accessible resources, including COSMIC (<http://www.sanger.ac.uk/cosmic>), which curates comprehensive information on somatic mutations in human cancer.⁴³ These resources are being utilized to determine the most common genomic alterations in common tumor types. This information is being integrated into clinical practice in many tumor types, such as lung cancer, where molecular drivers are being chosen taking into consideration in systemic therapy selection (Fig. 10-10).

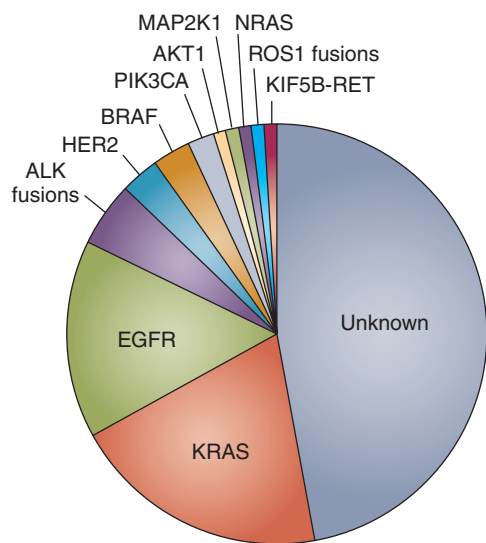


Figure 10-10. Molecular subsets of lung adenocarcinoma. Pie chart shows the percentage of tumors with each potentially actionable alteration. (Adapted by permission from Macmillan Publishers Ltd. Pao W, Hutchinson KE. Chipping away at the lung cancer genome. *Nat Med.* 2012;18:349. Copyright © 2012.)¹⁷²

Tumor Heterogeneity and Molecular Evolution

There is increasing recognition that tumors are heterogeneous; this represents an important challenge to utilizing genomic alterations to personalize cancer therapy (Fig. 10-11).⁴⁴ First, there is significant intertumoral heterogeneity, such that patients with tumors that seem similar histologically, may differ in genomic alterations and in malignant potential.⁴⁵⁻⁴⁷ Second, during cancer progression, subclones frequently arise, resulting in differences in the proportion and pattern of genomic alterations between the primary tumor and the metastases or local-regional recurrences.⁴⁴ Third, there may also be significant intratumoral heterogeneity, with spatially separated heterogeneous somatic mutations and chromosomal imbalances.⁴⁸ Such spatial heterogeneity of subclones within the primary tumor or metastases provides an additional challenge, as it has been proposed that

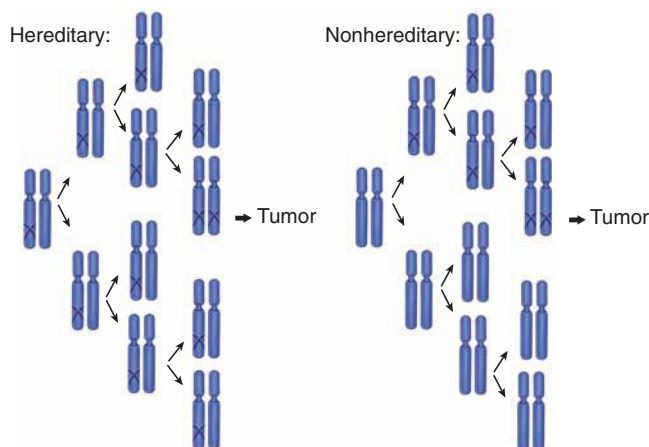


Figure 10-11. “Two-hit” tumor formation in both hereditary and nonhereditary cancers. A “one-hit” clone is a precursor to the tumor in nonhereditary cancer, whereas all cells are one-hit clones in hereditary cancer. (Adapted by permission from Macmillan Publishers Ltd. Knudson AG. Two genetic hits (more or less) to cancer. *Nat Rev Cancer.* 2001;1:157. Copyright © 2001.)⁵¹

sequencing of a biopsy specimen or only a portion of the tumor could miss therapeutically relevant genomic alterations. The genomic alterations found in a tumor can also change under the selective pressure of a targeted therapy, adding to the challenge of implementing genomically-informed personalized therapy.

Genes Associated with Hereditary Cancer Risk

Most of our information on human cancer genes has been gained from hereditary cancers. In the case of hereditary cancers, the individual carries a particular germline mutation in every cell. To date, over 70 genes have been associated with hereditary cancers (Table 10-3).⁴² A few of these hereditary cancer genes are oncogenes, but most are tumor-suppressor genes. Although hereditary cancer syndromes are rare, somatic mutations that occur in sporadic cancer have been found to disrupt the cellular pathways altered in hereditary cancer syndromes, which suggests that these pathways are critical to normal cell growth, cell cycle, and proliferation.

The following factors may suggest the presence of a hereditary cancer⁴⁹:

1. Tumor development at a much younger age than usual
2. Presence of bilateral disease
3. Presence of multiple primary malignancies
4. Presentation of a cancer in the less affected sex (e.g., male breast cancer)
5. Clustering of the same cancer type in relatives
6. Occurrence of cancer in association with other conditions such as mental retardation or pathognomonic skin lesions

It is crucial that all surgeons caring for cancer patients be aware of hereditary cancer syndromes, because a patient's genetic background has significant implications for patient counseling, planning of surgical therapy, and cancer screening and prevention. Some of the more commonly encountered hereditary cancer syndromes are discussed here.

rb1Gene. The retinoblastoma gene *rb1* was the first tumor suppressor to be cloned. The *rb1* gene product, the Rb protein, is a regulator of transcription that controls the cell cycle, differentiation, and apoptosis in normal development.⁵⁰ Retinoblastoma has long been known to occur in hereditary and nonhereditary forms. Interestingly, although most children with an affected parent develop bilateral retinoblastoma, some develop unilateral retinoblastoma. Furthermore, some children with an affected parent are not affected themselves but then have an affected child, which indicates that they are *rb1* mutation carriers. These findings led to the theory that a single mutation is not sufficient for tumorigenesis. Alfred Knudson hypothesized that hereditary retinoblastoma involves two mutations, of which one is germline and one somatic, whereas nonhereditary retinoblastoma is due to two somatic mutations (Fig. 10-12).⁵¹ Thus, both hereditary and nonhereditary forms of retinoblastoma involve the same number of mutations, a hypothesis known as Knudson's “two-hit” hypothesis. A “hit” may be a point mutation, a chromosomal deletion referred to as *allelic loss*, or a loss of heterozygosity, or silencing of an existing gene.

p53 and Li-Fraumeni Syndrome. Li-Fraumeni syndrome (LFS) was first defined on the basis of observed clustering of malignancies, including early-onset breast cancer, soft tissue sarcomas, brain tumors, adrenocortical tumors, and leukemia.⁵² Criteria for classic LFS in an individual (the proband) include:

Table 10-3

Selected genes associated with hereditary cancer

SYMBOL	NAME	TUMOR TYPES (GERMLINE MUTATIONS)	CANCER SYNDROME
ALK	anaplastic lymphoma kinase (Ki-1)	Neuroblastoma	Familial neuroblastoma
APC	adenomatous polyposis of the colon gene	Colorectal, pancreatic, desmoid, hepatoblastoma, glioma, other CNS	Adenomatous polyposis coli; Turcot syndrome
ATM	ataxia telangiectasia mutated	Leukemia, lymphoma, medulloblastoma, glioma	Ataxia-telangiectasia
BLM	Bloom Syndrome	Leukemia, lymphoma, skin squamous cell, other cancers	Bloom Syndrome
BMPRI1A	bone morphogenetic protein receptor, type IA	Gastrointestinal polyps	Juvenile polyposis
BRCA1	familial breast/ovarian cancer gene 1	Breast, ovarian	Hereditary breast/ovarian cancer
BRCA2	familial breast/ovarian cancer gene 2	Breast, ovarian, pancreatic	Hereditary breast/ovarian cancer
BRIP1	BRCA1 interacting protein C-terminal helicase 1	AML, leukemia, breast	Fanconi anaemia J, breast cancer susceptibility
BUB1B	BUB1 budding uninhibited by benzimidazoles 1 homolog beta (yeast)	Rhabdomyosarcoma	Mosaic variegated aneuploidy
CDH1	cadherin 1, type 1, E-cadherin (epithelial) (ECAD)	Gastric, lobular cancer	Familial gastric carcinoma
CDK4	cyclin-dependent kinase 4	Melanoma	Familial malignant melanoma
CDKN2A	cyclin-dependent kinase inhibitor 2A (p16(INK4a)) gene	Melanoma, pancreatic	Familial malignant melanoma
CDKN2a(p14)	cyclin-dependent kinase inhibitor 2A- p14ARF protein	Melanoma, pancreatic	Familial malignant melanoma
CHEK2	CHK2 checkpoint homolog (<i>S. pombe</i>)	Breast	Familial breast cancer
CYLD	familial cylindromatosis gene	Cylindroma	Familial cylindromatosis
DDB2	damage-specific DNA binding protein 2	Skin basal cell, skin squamous cell, melanoma	Xeroderma pigmentosum (E)
DICER1	dicer 1, ribonuclease type III	Pleuropulmonary blastoma	Familial Pleuropulmonary Blastoma
EGFR	epidermal growth factor receptor (erythroblastic leukemia viral (v-erb-b) oncogene homolog, avian)	NSCLC	Familial lung cancer
ERCC2, 3, 4, 5	excision repair cross-complementing rodent repair deficiency, complementation group	Skin basal cell, skin squamous cell, melanoma	Xeroderma pigmentosum (D, B, F, G))
EXT1	multiple exostoses type 1 gene	exostoses, osteosarcoma	exostoses, osteosarcoma
FANCA, C, D2, E, F, G	Fanconi anemia, complementation group	AML, leukemia	Fanconi anaemia A, C, D2, E, F, G
FH	fumarate hydratase	leiomyomatosis, renal	Hereditary leiomyomatosis and renal cell cancer
GPC3	glypican 3	Wilms' tumor	Simpson-Golabi-Behmel syndrome
HRAS	v-Ha-ras Harvey rat sarcoma viral oncogene homolog	v-Ha-ras Harvey rat sarcoma viral oncogene homolog	Costello syndrome
HRPT2	Hyperparathyroidism 2 (parafibromin)	parathyroid adenoma, multiple ossifying jaw fibroma	Hyperparathyroidism-jaw tumor syndrome
KIT	v-kit Hardy-Zuckerman 4 feline sarcoma viral oncogene homolog	GIST, epithelioma	Familial gastrointestinal stromal tumor

Table 10-3

Selected genes associated with hereditary cancer (continued)

SYMBOL	NAME	TUMOR TYPES (GERMLINE MUTATIONS)	CANCER SYNDROME
MADH4	Homolog of <i>Drosophila</i> Mothers Against Decapentaplegic 4 gene	Gastrointestinal polyps	Juvenile polyposis
MEN1	multiple endocrine neoplasia type 1 gene	Parathyroid adenoma, pituitary adenoma, pancreatic islet cell, carcinoid	Parathyroid adenoma, pituitary adenoma, pancreatic islet cell, carcinoid
MLH1	<i>E. coli</i> MutL homolog gene	Colorectal, endometrial, ovarian, CNS	Hereditary nonpolyposis colorectal cancer, Turcot syndrome
MPL	myeloproliferative leukemia virus oncogene, thrombopoietin receptor	MPD	Familial essential thrombocythemia
MSH2	mutS homolog 2 (<i>E. coli</i>)	colorectal, endometrial, ovarian	Hereditary non-polyposis colorectal cancer
MSH6	mutS homolog 6 (<i>E. coli</i>)	colorectal, endometrial, ovarian	Hereditary non-polyposis colorectal cancer
MUTYH	mutY homolog (<i>E. coli</i>)	Colorectal	Adenomatous polyposis coli
NBS1	Nijmegen breakage syndrome 1 (nibrin)	NHL, glioma, medulloblastoma, rhabdomyosarcoma	Nijmegen breakage syndrome
NF1	neurofibromatosis type 1 gene	Neurofibroma, glioma	Neurofibromatosis type 1
NF2	neurofibromatosis type 2 gene	Meningioma, acoustic neuroma	Neurofibromatosis type 2
PALB2	partner and localizer of BRCA2	Wilms tumor, medulloblastoma, AML, breast	Fanconi anaemia N, breast cancer susceptibility
PHOX2B	paired-like homeobox 2b	Neuroblastoma	Familial neuroblastoma
PMS1	PMS1 postmeiotic segregation increased 1 (<i>S. cerevisiae</i>)	Colorectal, endometrial, ovarian	Hereditary non-polyposis colorectal cancer
PMS2	PMS2 postmeiotic segregation increased 2 (<i>S. cerevisiae</i>)	Colorectal, endometrial, ovarian, medulloblastoma, glioma	Hereditary nonpolyposis colorectal cancer, Turcot syndrome
PRKAR1A	protein kinase, cAMP-dependent, regulatory, type I, alpha (tissue specific extinguisher 1)	Myxoma, endocrine, papillary thyroid	Carney complex
PTCH	Homolog of <i>Drosophila</i> Patched gene	Skin basal cell, medulloblastoma	Nevoid Basal Cell Carcinoma Syndrome
PTEN	phosphatase and tensin homolog gene	Hamartoma, glioma, prostate, endometrial	Cowden Syndrome, Bannayan-Riley-Ruvalcaba syndrome
RB1	retinoblastoma gene	Retinoblastoma, sarcoma, breast, small cell lung	Familial retinoblastoma
RECQL4	RecQ protein-like 4	Osteosarcoma, skin basal and squamous cell	Rothmund-Thompson Syndrome
RET	ret proto-oncogene	Medullary thyroid, papillary thyroid, pheochromocytoma	Multiple endocrine neoplasia 2A/2B
SBDS	Shwachman-Bodian-Diamond syndrome protein	AML, MDS	Schwachman-Diamond syndrome
SDH5	chromosome 11 open reading frame 79	Paraganglioma	Familial paraganglioma
SHD, B, D	succinate dehydrogenase complex	Paraganglioma, pheochromocytoma	Familial paraganglioma

(Continued)

Table 10-3

Selected genes associated with hereditary cancer (continued)

SYMBOL	NAME	TUMOR TYPES (GERMLINE MUTATIONS)	CANCER SYNDROME
SMARCB1	SWI/SNF related, matrix associated, actin dependent regulator of chromatin, subfamily b, member 1	Malignant rhabdoid	Rhabdoid predisposition syndrome
STK11	serine/threonine kinase 11 gene (LKB1)	Jejunal hamartoma, ovarian, testicular, pancreatic	Peutz-Jeghers syndrome
SUFU	suppressor of fused homolog (<i>Drosophila</i>)	Medulloblastoma	Medulloblastoma predisposition
TCF1	transcription factor 1, hepatic (HNF1)	Hepatic adenoma, hepatocellular carcinoma	Familial Hepatic Adenoma
TP53	tumor protein p53	Breast, sarcoma, adrenocortical carcinoma, glioma, multiple other tumor types	Li-Fraumeni syndrome
TSC1	tuberous sclerosis 1 gene	Hamartoma, renal cell	Tuberous sclerosis 1
TSC2	tuberous sclerosis 2 gene	Hamartoma, renal cell	Tuberous sclerosis 2
TSHR	thyroid stimulating hormone receptor	Thyroid adenoma	
VHL	von Hippel-Lindau syndrome gene	Renal, hemangioma, pheochromocytoma	von Hippel-Lindau syndrome
WRN	Werner syndrome (RECQL2)	Osteosarcoma, meningioma, others	Werner Syndrome
WT1	Wilms' tumor 1 gene	Wilms'	Denys-Drash syndrome, Frasier syndrome, Familial Wilms tumor
XPA, C	xeroderma pigmentosum, complementation group	Skin basal cell, skin squamous cell, melanoma	Xeroderma pigmentosum (A C)

A, amplification; AEL, acute eosinophilic leukemia; AL, acute leukemia; ALCL, anaplastic large-cell lymphoma; ALL, acute lymphocytic leukemia; AML, acute myelogenous leukemia; AML*, acute myelogenous leukemia (primarily treatment associated); APL, acute promyelocytic leukemia; B-ALL, B-cell acute lymphocytic leukaemia; B-CLL, B-cell Lymphocytic leukemia; B-NHL, B-cell Non-Hodgkin Lymphoma; CLL, chronic lymphatic leukemia; CML, chronic myeloid leukemia; CMML, chronic myelomonocytic leukemia; CNS, central nervous system; D, large deletion; DFSP, dermatofibrosarcoma protuberans; DLBL, diffuse large B-cell lymphoma; DLCL, diffuse large-cell lymphoma; Dom, dominant; E, epithelial; F, frameshift; GIST, gastrointestinal stromal tumour; JMML, juvenile myelomonocytic leukemia; L, leukaemia/lymphoma; M, mesenchymal; MALT, mucosa-associated lymphoid tissue lymphoma; MDS, myelodysplastic syndrome; Mis, Missense; MLCLS, mediastinal large cell lymphoma with sclerosis; MM, multiple myeloma; MPD, Myeloproliferative disorder; N, nonsense; NHL, non-Hodgkin lymphoma; NK/T, natural killer T cell; NSCLC, non small cell lung cancer; O, other; PMBL, primary mediastinal B-cell lymphoma; pre-B All, pre-B-cell acute lymphoblastic leukaemia; Rec, recessive; S, splice site; T, translocation; T-ALL, T-cell acute lymphoblastic leukemia; T-CLL, T-cell chronic lymphocytic leukaemia; TGCT, testicular germ cell tumour; T-PLL, T cell prolymphocytic leukemia

Source: Adapted by permission from Macmillan Publishers Ltd. Futreal PA et al. A census of human cancer genes. Nat Rev Cancer. 2004;4:177. Copyright © 2004.

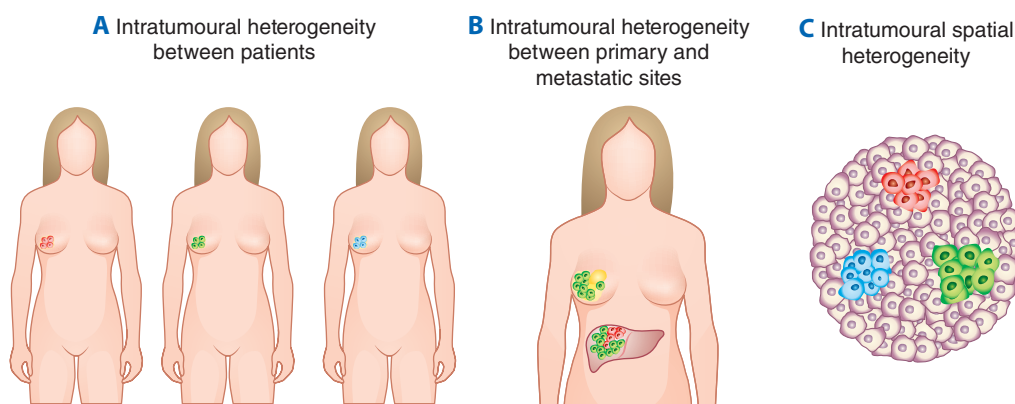


Figure 10-12. Tumor heterogeneity. **A.** Patients with tumors with similar histologies may differ in genetic mutation status and other molecular features **B.** Cells within the primary tumor can acquire or lose genomic alterations in metastatic sites. **C.** Intratumoural spatial heterogeneity: common initiating genomic events usually exist in all tumor cells but additional spatially separated heterogeneous somatic mutations or copy number changes may accumulate. (Adapted with permission from Meric-Bernstam and Mills)⁴⁴

(a) a bone or soft tissue sarcoma when younger than 45 years, (b) a first-degree relative with cancer before age 45 years, and (c) another first- or second-degree relative with either a sarcoma diagnosed at any age or any cancer diagnosed before age 45 years.⁵³ Approximately 70% of LFS families have been shown to have germline mutations in the tumor-suppressor gene p53.⁵⁴ Breast carcinoma, soft tissue sarcoma, osteosarcoma, brain tumors, adrenocortical carcinoma, Wilms' tumor, and phyllodes tumor of the breast are strongly associated; pancreatic cancer is moderately associated; and leukemia and neuroblastoma are weakly associated with germline p53 mutations.⁵⁵ Mutations of p53 have not been detected in approximately 30% of LFS families, and it is hypothesized that genetic alterations in other proteins interacting with p53 function may play a role in these families.

Of the known genes in human cancer, p53 is the most commonly mutated. The p53 protein regulates cell-cycle progression as well as apoptotic cell death as part of stress response pathways after exposure to ionizing or ultraviolet (UV) irradiation, chemotherapy, acidosis, growth factor deprivation, or hypoxia. When cells are exposed to stressors, p53 acts as a transcription factor for genes that induce cell-cycle arrest or apoptosis. A majority of p53 mutations are found within a central DNA recognition motif and disrupt DNA binding by p53. Families with germline missense mutations in the DNA-binding domain show a more highly penetrant phenotype than families with other p53 mutations.⁵⁶ Furthermore, proband cancers are linked with significantly younger age at diagnosis in patients with missense mutations in the DNA-binding domain.⁵⁶

BRCA1, BRCA2, and Hereditary Breast-Ovarian Cancer

Syndromes. It is estimated that 5% to 10% of breast cancers are hereditary. Of women with early-onset breast cancer (aged 40 years or younger), nearly 10% have a germline mutation in one of the breast cancer genes *BRCA1* or *BRCA2*.⁵⁷ Mutation carriers are more prevalent among women who have a first- or second-degree relative with premenopausal breast cancer or ovarian cancer at any age. The likelihood of a *BRCA* mutation is higher in patients who belong to a population in which founder mutations may be prevalent, such as in the Ashkenazi Jewish population. For a female *BRCA1* mutation carrier, the cumulative risks of developing breast cancer and ovarian cancer by age 70 have been estimated to be 87% and 44%, respectively.⁵⁸ The cumulative risks of breast cancer and ovarian cancer by age 70 in families with *BRCA2* mutation have been estimated to be 84% and 27%, respectively.⁵⁹ Although male breast cancer can occur with either *BRCA1* or *BRCA2* mutation, the majority of families (76%) with both male and female breast cancer have mutations in *BRCA2*.⁵⁹ Besides breast and ovarian cancer, *BRCA1* and *BRCA2* mutations may be associated with increased risks for several other cancers. *BRCA1* mutations confer a fourfold increased risk for colon cancer and threefold increased risk for prostate cancer.⁵⁸ *BRCA2* mutations confer a fivefold increased risk for prostate cancer, sevenfold in men younger than 65 years.⁶⁰ Furthermore, *BRCA2* mutations confer a fivefold increased risk for gallbladder and bile duct cancers, fourfold increased risk for pancreatic cancer, and threefold increased risk for gastric cancer and malignant melanoma.⁶⁰

BRCA1 was the first breast cancer susceptibility gene identified and has been mapped to 17q21. *BRCA2*, mapped to 13q12.3, was reported shortly afterward. *BRCA1* and *BRCA2*

encode large nuclear proteins, 208 kDa and 384 kDa, respectively, that have been implicated in processes fundamental to all cells, including DNA repair and recombination, checkpoint control of the cell cycle, and transcription.⁶¹ Although early studies suggested that the two proteins function together as a complex, subsequent data demonstrated that they have distinct functions.^{62, 63} In fact, breast cancers arising from *BRCA1* or *BRCA2* mutations are different at the molecular level and have been found to have distinct gene expression profiles.⁶⁴ *BRCA1*-associated tumors are more likely to be estrogen receptor negative, whereas *BRCA2*-associated tumors are more likely to be estrogen receptor positive. Currently, studies are ongoing to determine whether *BRCA1* and *BRCA2* status can be used to guide systemic therapy choices for breast cancer.

APC Gene and Familial Adenomatous Polyposis

Patients affected with familial adenomatous polyposis (FAP) characteristically develop hundreds to thousands of polyps in the colon and rectum. The polyps usually appear in adolescence and, if left untreated, progress to colorectal cancer. FAP is associated with benign extracolonic manifestations that may be useful in identifying new cases, including congenital hypertrophy of the retinal pigment epithelium, epidermoid cysts, and osteomas. In addition to colorectal cancer, patients with FAP are at risk for upper intestinal neoplasms (gastric and duodenal polyps, duodenal and periampullary cancer), hepatobiliary tumors (hepatoblastoma, pancreatic cancer, and cholangiocarcinoma), thyroid carcinomas, desmoid tumors, and medulloblastomas.

The product of the adenomatous polyposis coli tumor-suppressor gene (*APC*) plays an important role in cell-cell interactions, cell adhesion, regulation of β -catenin, and maintenance of cytoskeletal microtubules. Alterations in *APC* lead to dysregulation of several physiologic processes that govern colonic epithelial cell homeostasis, including cell-cycle progression, migration, differentiation, and apoptosis. Mutations in the *APC* have been identified in FAP and in 80% of sporadic colorectal cancers.⁶⁵ Furthermore, *APC* mutations are the earliest known genetic alterations in colorectal cancer progression, which emphasizes its importance in cancer initiation. The germline mutations in *APC* may arise from point mutations, insertions, or deletions that lead to a premature stop codon and a truncated, functionally inactive protein. The risk of developing specific manifestations of FAP is correlated with the position of the *APC* mutations, a phenomenon referred to as *genotype-phenotype correlation*. For example, desmoids usually are associated with mutations between codons 1403 and 1578.^{66, 67} Mutations in the extreme 5' or 3' ends of *APC*, or in the alternatively spliced region of exon 9, are associated with an attenuated version of FAP. Better understanding of the genotype-phenotype correlations may assist in patient counseling and therapeutic planning.

Mismatch Repair Genes and Hereditary Nonpolyposis Colorectal Cancer.

Hereditary nonpolyposis colorectal cancer (HNPCC), also referred to as *Lynch syndrome*, is an autosomal dominant hereditary cancer syndrome that predisposes to a wide spectrum of cancers, including colorectal cancer without polyposis. Some have proposed that HNPCC consists of at least two syndromes: Lynch syndrome 1, which entails hereditary predisposition for colorectal cancer with early age of onset (approximately age 44 years) and an excess of synchronous and metachronous colonic cancers; and Lynch syndrome 2, featuring a similar colonic phenotype accompanied by a high risk

Table 10-4

Revised criteria for hereditary nonpolyposis colon cancer (HNPCC) (Amsterdam criteria II)

Three or more relatives with an HNPCC-associated cancer (colorectal cancer, endometrial cancer, cancer of the small bowel, ureter, or renal pelvis), one of whom is a first-degree relative of the other two
 At least two successive generations affected
 At least one case diagnosed before age 50 y
 Familial adenomatous polyposis excluded
 Tumors verified by pathologic examination

Source: Modified with permission from Vasen et al. Copyright Elsevier.⁶⁹

for carcinoma of the endometrium, transitional cell carcinoma of the ureter and renal pelvis, and carcinomas of the stomach, small bowel, ovary, and pancreas.⁶⁸ The diagnostic criteria for HNPCC are referred to as the *Amsterdam criteria*, or the *3-2-1-0 rule*. The classic Amsterdam criteria were revised to include other HNPCC-related cancers (Table 10-4).⁶⁹ These criteria are met when three or more family members have histologically verified, HNPCC-associated cancers (one of whom is a first-degree relative of the other two), two or more generations are involved, at least one individual was diagnosed before age 50 years, and no individuals have FAP.⁶⁹

During DNA replication, DNA polymerases may introduce single nucleotide mismatches or small insertion or deletion loops. These errors are corrected through a process referred to as *mismatch repair*. When mismatch repair genes are inactivated, DNA mutations in other genes that are critical to cell growth and proliferation accumulate rapidly. In HNPCC, germline mutations have been identified in several genes that play a key role in DNA nucleotide mismatch repair: *hMLH1* (human mutL homologue 1), *hMSH2* (human mutS homologue 2), *hMSH6*, and *hPMS1* and *hPMS2* (human post-meiotic segregation 1 and 2), of which *hMLH1* and *hMSH2* are the most common.⁷⁰⁻⁷⁵ The hallmark of HNPCC is microsatellite instability, which occurs on the basis of unrepaired mismatches and small insertion or deletion loops. Microsatellite instability can be tested by comparing the DNA of a patient's tumor with DNA from adjacent normal epithelium, amplifying the DNA with polymerase chain reaction (PCR) using a standard set of markers, comparing the amplified genomic DNA sequences, and classifying the degree of microsatellite instability as high, low, or stable. Such microsatellite instability testing may help select patients who are more likely to have germline mutations.

PTEN and Cowden Disease

Somatic deletions or mutations in the tumor-suppressor gene *PTEN* (phosphatase and tensin homologue deleted on chromosome 10) have been observed in a number of glioma breast, prostate, and renal carcinoma cell lines and several primary tumor specimens.⁷⁶

PTEN encodes a 403-amino-acid protein, tyrosine phosphatase. *PTEN* negatively controls the PI3K signaling pathway for the regulation of cell growth and survival by dephosphorylating

phosphoinositol 3,4,5-triphosphate; thus mutation of *PTEN* leads to constitutive activation of the PI3K/Akt signaling pathway. The “hot spot” for *PTEN* mutations has been identified in exon 5. Forty-three percent of CD mutations have been identified in this exon, which contains the tyrosine phosphatase core domain. This suggests that the *PTEN* catalytic activity is vital for its biologic function. *PTEN* was identified as the susceptibility gene for the autosomal dominant syndrome Cowden disease (CD) or multiple hamartoma syndrome.⁷⁷ Trichilemmomas, benign tumors of the hair follicle infundibulum, and mucocutaneous papillomatosis are pathognomonic of CD. Other common features include thyroid adenomas and multinodular goiters, breast fibroadenomas, and hamartomatous GI polyps. The diagnosis of CD is made when an individual or family has a combination of pathognomonic major and/or minor criteria proposed by the International Cowden Consortium.⁷⁸ CD is associated with an increased risk of breast and thyroid cancers. Breast cancer develops in 25% to 50% of affected women.⁷⁸

p16 and Hereditary Malignant Melanoma. The gene p16, also known as *INK4A*, *CDKN1*, *CDKN2A*, and *MTS1*, is a tumor suppressor that acts by binding CDK4 and CDK6 and inhibiting the catalytic activity of the CDK4-CDK6/cyclin D complex that is required for phosphorylation of Rb and subsequent cell-cycle progression. Studies suggest that germline mutations in p16 can be found in 20% of melanoma-prone families.⁷⁹ Mutations in p16 that alter its ability to inhibit the catalytic activity of the CDK4-CDK6/cyclin D complex not only increase the risk of melanoma by 75-fold but also increase the risk of pancreatic cancer by 22-fold.⁸⁰ Interestingly, p16 mutations that do not appear to alter its function increase the risk of melanoma by 38-fold and do not increase the risk of pancreatic cancer.⁸⁰ Genomic characterization of primary tumors has revealed that p16 is inactivated through point mutation, promoter methylation, or deletion in a significant portion of sporadic tumors, including cancers of the pancreas, esophagus, head and neck, stomach, breast, and colon, as well as melanomas.

E-cadherin and Hereditary Diffuse Gastric Cancer. E-cadherin is a cell adhesion molecule that plays an important role in normal architecture and function of epithelial cells. The adhesive function of E-cadherin is dependent on interaction of its cytoplasmic domain with β - and γ -catenins and may be regulated by phosphorylation of β -catenin.

Hereditary diffuse gastric carcinoma is an autosomal dominant cancer syndrome that results from germline mutations in the E-cadherin gene, *CDH1*. Carriers of *CDH1* mutations have a 70% to 80% chance of developing gastric cancer.⁸¹ Furthermore, mutations of *CDH1* have been described in sporadic cancers of the ovary, endometrium, breast, and thyroid. However, frequent mutations have been identified in only two particular tumors: diffuse gastric carcinomas and lobular breast carcinomas. Invasive lobular breast carcinomas often show inactivating mutations in combination with a loss of heterozygosity of the wild-type *CDH1* allele.⁸² Interestingly, in gastric carcinomas the predominant mutations are exon skipping causing in-frame deletions, whereas most mutations identified in lobular breast cancers are premature stop codons; this suggests a genotype-phenotype correlation.

RET Proto-Oncogene and Multiple Endocrine Neoplasia Type 2

The *RET* (rearranged during transfection) gene encodes for a transmembrane receptor tyrosine kinase that plays a role in proliferation, migration, and differentiation of cells derived from the neural crest. Gain-of-function mutations in the *RET* gene are associated with medullary thyroid carcinoma in isolation or multiple endocrine neoplasia type 2 (MEN2) syndromes. MEN2A is associated with medullary thyroid carcinoma and pheochromocytoma (in 50%) or parathyroid adenoma (in 20%), whereas MEN2B is associated with medullary thyroid carcinoma, marfanoid habitus, mucosal neuromas, and ganglioneuromatosis.⁸³ *RET* mutations lead to uncontrolled growth of the thyroid C cells, and in familial medullary cancer, C-cell hyperplasia progresses to bilateral, multicentric medullary thyroid cancer. Mutations in the *RET* gene have also been identified in half of sporadic medullary thyroid cancers.

Genetic Modifiers of Risk. Individuals carrying identical germline mutations vary in regard to cancer penetrance (whether cancer will develop or not) and cancer phenotype (the tissues involved). It is thought that this variability may be due to environmental influences or, if genetic, to genetic modifiers of risk. Similarly, genetic modifiers of risk also can play a role in determining whether an individual will develop cancer after exposure to carcinogens.

Chemical Carcinogens

The first report indicating that cancer could be caused by environmental factors was by John Hill, who in 1761 noted the association between nasal cancer and excessive use of tobacco snuff.⁸⁴ Currently, approximately 60% to 90% of cancers are thought to be due to environmental factors. Any agent that can contribute to tumor formation is referred to as a *carcinogen* and can be a chemical, physical, or viral agent. Chemicals are classified into three groups based on how they contribute to tumor formation. The first group of chemical agents, the genotoxins, can initiate carcinogenesis by causing a mutation. The second group, the cocarcinogens, by themselves cannot cause cancer but potentiate carcinogenesis by enhancing the potency of genotoxins. The third group, tumor promoters, enhances tumor formation when given after exposure to genotoxins.

The International Agency for Research on Cancer (IARC) maintains a registry of human carcinogens that is available through the World Wide Web (<http://www.iarc.fr>). The compounds are categorized into five groups based on an analysis of epidemiologic studies, animal models, and short-term mutagenesis tests. Group 1 contains what are considered to be proven human carcinogens, based on formal epidemiologic studies among workers who were exposed for long periods (several years) to the chemicals.⁸⁵ Group 2A contains what are considered to be probable human carcinogens. Suggestive epidemiologic evidence exists for compounds in this group, but the data are insufficient to establish causality. There is evidence of carcinogenicity, however, from animal studies carried out under conditions relevant to human exposure. Group 2B contains what are considered to be possible carcinogens, because these substances are associated with a clear statistically and biologically significant increase in the incidence of malignant tumors in more than one animal species or strain. Group 3 agents are not classifiable, and Group 4 agents are probably not carcinogenic to humans.

Selected substances that have been classified as proven carcinogens (group 1) by the IARC in an expert panel review in 2009 are listed in Table 10-5.⁸⁶

Physical Carcinogens

Physical carcinogenesis can occur through induction of inflammation and cell proliferation over a period of time or through exposure to physical agents that induce DNA damage. Foreign bodies can cause chronic irritation that can expose cells to carcinogenesis due to other environmental agents. In animal models, for example, subcutaneous implantation of a foreign body can lead to the development of tumors that have been attributed to chronic irritation from the foreign objects. In humans, clinical scenarios associated with chronic irritation and inflammation such as chronic nonhealing wounds, burns, and inflammatory bowel syndrome have all been associated with an increased risk of cancer. *H. pylori* infection is associated with gastritis and gastric cancer, and thus, its carcinogenicity may be considered physical carcinogenesis. Infection with the liver fluke *Opisthorchis viverrini* similarly leads to local inflammation and cholangiocarcinoma.

The induction of lung and mesothelial cancers by asbestos fibers and nonfibrous particles such as silica are other examples of foreign body-induced physical carcinogenesis.⁸⁷ Animal experiments have demonstrated that the dimensions and durability of the asbestos and other fibrous minerals are the key determinants of their carcinogenicity.⁸⁸ Short fibers can be inactivated by phagocytosis, whereas long fibers (>10 μ m) are cleared less effectively and are encompassed by proliferating epithelial cells. The long fibers support cell proliferation and have been shown to preferentially induce tumors. Asbestos-associated biologic effects also may be mediated through reactive oxygen and nitrogen species. Furthermore, an interaction occurs between asbestos and silica and components of cigarette smoke. Polycyclic aromatic hydrocarbons (PAHs) in cigarette smoke are metabolized by epithelial cells and form DNA adducts. If PAH is coated on asbestos, PAH uptake is increased.⁸⁷ Both PAH and asbestos impair lung clearance, potentially increasing uptake further. Therefore, physical carcinogens may be synergistic with chemical carcinogens.

Radiation is the best-known agent of physical carcinogens and is classified as ionizing radiation (X-rays, gamma rays, and alpha and beta particles) or nonionizing radiation (UV). The carcinogenic potential of ionizing radiation was recognized soon after Wilhelm Conrad Roentgen's discovery of X-rays in 1895. Within the next 20 years, a large number of radiation-related skin cancers were reported. Long-term follow-up of survivors of the atomic bombing of Hiroshima and Nagasaki revealed that virtually all tissues exposed to radiation are at risk for cancer.

Radiation can induce a spectrum of DNA lesions that includes damage to the nucleotide bases and cross-linking, and DNA single- and double-strand breaks (DSBs). Misrepaired DSBs are the principal lesions of importance in the induction of chromosomal abnormalities and gene mutations. DSBs in irradiated cells are repaired primarily by a nonhomologous end-joining process, which is error prone; thus, DSBs facilitate the production of chromosomal rearrangements and other large-scale changes such as chromosomal deletions. It is thought that radiation may initiate cancer by inactivating tumor-suppressor genes. Activation of oncogenes appears to play a lesser role in radiation carcinogenesis.

Table 10-5

Group 1 chemical carcinogens and evidence for carcinogenicity in humans and for genotoxicity as the main mechanism

	TUMOR SITES OR TYPES WITH SUFFICIENT EVIDENCE IN HUMANS	EVIDENCE OF GENOTOXICITY AS THE MAIN MECHANISM
4-Aminobiphenyl	Urinary bladder	Strong
Benzidine	Urinary bladder	Strong
Dyes metabolized to benzidine	..	Strong*
4,4'-Methylenebis(2-chloroaniline)	..	Strong*
2-Naphthylamine	Urinary bladder	Strong
Ortho-toluidine	Urinary bladder	Moderate
Auramine production	Urinary bladder	Weak/lack of data†
Magenta production	Urinary bladder	Weak/lack of data†
Benzo[α]pyrene	..	Strong*
Soot (chimney sweeping)	Skin, lung	Moderate
Coal gasification	Lung	Strong
Coal-tar distillation	Skin	Strong
Coke production	Lung	Strong
Coal-tar pitches (paving, roofing)	Lung	Strong
Aluminum production	Lung, urinary bladder	Weak/moderate†‡
Aflatoxins	Hepatocellular carcinoma	Strong
Benzene	ANLL	Strong
Bis(chloromethyl)ether/ chloromethyl methylether	Lung	Moderate/strong
1,3-Butadiene	Haematolymphatic organs	Strong
Dioxin (2,3,7,8-TCDD)	All cancers combined**	See text§
2,3,4,7,8-Pentachlorodibenzofuran	..	See text*§
3,3',4,4',5-Pentachlorobiphenyl (PCB-126)	..	See text*§
Ethylene oxide	..	Strong*
Formaldehyde	Nasopharynx Leukemia**	Strong Moderate
Sulfur mustard	Lung	Strong
Vinyl chloride	Hepatic angiosarcoma, hepatocellular carcinoma	Strong
Iron and steel founding	Lung	Weak/moderate
Isopropyl alcohol manufacture using strong acids	Nasal cavity	Weak/lack of data
Mineral oils	Skin	Weak/lack of data
Occupational exposure as a painter	Lung, urinary bladder, pleural mesothelioma	Strong‡
Rubber-manufacturing industry	Leukaemia**, lymphoma**, urinary bladder, lung**, stomach**	Strong‡
Shale oils	Skin	Weak/lack of data
Strong inorganic acid mists	Larynx	Weak/lack of data

ANLL, acute non-lymphocytic leukaemia; ALL, acute lymphocytic leukaemia; CLL, chronic lymphocytic leukaemia; MM, multiple myeloma; NHL, non-Hodgkin lymphoma; STS, soft-tissue sarcoma.

*Agents classified in Group 1 on the basis of mechanistic information.

†Weak evidence in workers, but strong evidence for some chemicals in this industry.

‡Due to the diversity and complexity of these exposures, other mechanisms may also be relevant.

§Strong evidence for an aryl hydrocarbon receptor (AhR)-mediated mechanism.

¶Particularly myeloid leukemia.

||After maternal exposure (before or during pregnancy, or both).

**New epidemiological findings.

Source: Adapted from Baan et al 2009. Copyright Elsevier.⁸⁶

Although it has been assumed that the initial genetic events induced by radiation constitute direct mutagenesis from radiation, other indirect effects may contribute to carcinogenesis. For example, radiation induces genomic instability in cells that persists for at least 30 generations after irradiation. Therefore, even if cells do not acquire mutations at initial irradiation, they remain at risk for developing new mutations for several generations. Moreover, even cells that have not been directly irradiated appear to be at risk, a phenomenon referred to as the *bystander effect*.

Nonionizing UV radiation is a potent DNA-damaging agent and is known to induce skin cancer in experimental animals. Most nonmelanoma human skin cancers are thought to be induced by repeated exposure to sunlight, which leads to a series of mutations that allow the cells to escape normal growth control. Patients with inherited xeroderma pigmentosum lack one or more DNA repair pathways, which confers susceptibility to UV-induced cancers, especially on sun-exposed body parts. Patients with ataxia telangiectasia mutated syndrome also have a radiation-sensitive phenotype.

Viral Carcinogens

One of the first observations that cancer may be caused by transmissible agents was by Peyton Rous in 1910 when he demonstrated that cell-free extracts from sarcomas in chickens could transmit sarcomas to other animals injected with these extracts.⁸⁹ This was subsequently discovered to represent viral transmission of cancer by the Rous sarcoma virus. At present, several human viruses are known to have oncogenic properties, and several have been causally linked to human cancers (Table 10-6).⁸⁵ It is estimated that 15% of all human tumors worldwide are caused by viruses.⁹⁰

Table 10-6

Selected viral carcinogens^a

VIRUS	PREDOMINANT TUMOR TYPE ^b
Epstein-Barr virus	Burkitt's lymphoma
	Hodgkin's disease
	Immunosuppression-related lymphoma
	Sinonasal angiocentric T-cell lymphoma
	Nasopharyngeal carcinoma
Hepatitis B virus	Hepatocellular carcinoma
Hepatitis C virus	Hepatocellular carcinoma
HIV type 1	Kaposi's sarcoma
	Non-Hodgkin's lymphoma
Human papillomavirus 16 and 18	Cervical cancer
	Anal cancer
Human T-cell lymphotropic viruses	Adult T-cell leukemia/lymphoma

^aData based on information in the International Agency for Research on Cancer monographs.⁸⁵

^bOnly tumor types for which causal relationships are established are listed. Other cancer types may be linked to the agents with a lower frequency or with insufficient data to prove causality.

Viruses may cause or increase the risk of malignancy through several mechanisms, including direct transformation, expression of oncogenes that interfere with cell-cycle checkpoints or DNA repair, expression of cytokines or other growth factors, and alteration of the immune system. Oncogenic viruses may be RNA or DNA viruses. Oncogenic RNA viruses are retroviruses and contain a reverse transcriptase. After the viral infection, the single-stranded RNA viral genome is transcribed into a double-stranded DNA copy, which is then integrated into the chromosomal DNA of the cell. Retroviral infection of the cell is permanent; thus, integrated DNA sequences remain in the host chromosome. Oncogenic transforming retroviruses carry oncogenes derived from cellular genes. These cellular genes, referred to as *proto-oncogenes*, usually are involved in mitogenic signaling and growth control, and include protein kinases, G proteins, growth factors, and transcription factors (Table 10-7).⁹⁰

Integration of the provirus upstream of a proto-oncogene may produce chimeric virus-cell transcripts and recombination during the next round of replication that could lead to incorporation of the cellular gene into the viral genome.⁹⁰ Then again, many retroviruses do not possess oncogenes but can cause tumors in animals regardless. This occurs by integration of the provirus near a normal cellular proto-oncogene and activation of the expression of these genes by the strong promoter and enhancer sequences in the integrated viral sequence.

Unlike the oncogenes of the RNA viruses, those of the DNA tumor viruses are viral, not cellular, in origin. These genes are required for viral replication using the host cell machinery. In permissive hosts, infection with an oncogenic DNA virus may result in a productive lytic infection, which leads to cell death and the release of newly formed viruses. In nonpermissive cells, the viral DNA can be integrated into the cellular chromosomal DNA, and some of the early viral genes can be synthesized persistently, which leads to transformation of cells to a neoplastic state. The binding of viral oncoproteins to cellular tumor-suppressor proteins p53 and Rb is fundamental to the carcinogenesis induced by most DNA viruses, although some target different cellular proteins.

Like other types of carcinogenesis, viral carcinogenesis is a multistep process. Some retroviruses contain two cellular oncogenes, rather than one, in their genome and are more rapidly tumorigenic than single-gene transforming retroviruses, which emphasizes the cooperation between transforming genes. Furthermore, some viruses encode genes that suppress or delay apoptosis.

Although immunocompromised individuals are at elevated risk, most patients infected with oncogenic viruses do not develop cancer. When cancer does develop, it usually occurs several years after the viral infection. It is estimated, for example, that the risk of hepatocellular carcinoma (HCC) among individuals infected with hepatitis C virus is 1% to 3% after 30 years.⁹¹ There may be synergy between various environmental factors and viruses in carcinogenesis.

Recognition of a viral origin for some tumors has led to the pursuit of vaccination as a preventive strategy. The use of childhood hepatitis B vaccination has already translated into a decrease in liver cancer incidence in the Far East.⁵ Similarly, it is recognized that cervical cancer and its obligate precursors, cervical intraepithelial neoplasia grades 2 and 3, and adenocarcinoma in situ, are caused by oncogenic human papillomavirus (HPV); administration of HPV vaccine to HPV-naïve women,

Table 10-7

Selected cellular oncogenes in retroviruses

ONCOGENE	VIRUS NAME	ORIGIN	PROTEIN PRODUCT
<i>abl</i>	Abelson murine leukemia virus	Mouse	Tyrosine kinase
<i>fes</i>	ST feline sarcoma virus	Cat	Tyrosine kinase
<i>fps</i>	Fujinami sarcoma virus	Chicken	Tyrosine kinase
<i>src</i>	Rous sarcoma virus	Chicken	Tyrosine kinase
<i>erbB</i>	Avian erythroblastosis virus	Chicken	Epidermal growth factor receptor
<i>fms</i>	McDonough feline sarcoma virus	Cat	Colony-stimulating factor receptor
<i>kit</i>	Hardy-Zuckerman 4 feline sarcoma virus	Cat	Stem cell factor receptor
<i>mil</i>	Avian myelocytoma virus	Chicken	Serine/threonine kinase
<i>mos</i>	Moloney murine sarcoma virus	Mouse	Serine/threonine kinase
<i>raf</i>	Murine sarcoma virus 3611	Mouse	Serine/threonine kinase
<i>sis</i>	Simian sarcoma virus	Monkey	Platelet-derived growth factor
<i>H-ras</i>	Harvey murine sarcoma virus	Rat	GDP/GTP binding
<i>K-ras</i>	Kirsten murine sarcoma virus	Rat	GDP/GTP binding
<i>erbA</i>	Avian erythroblastosis virus	Chicken	Transcription factor (thyroid hormone receptor)
<i>ets</i>	Avian myeloblastosis virus E26	Chicken	Transcription factor
<i>fos</i>	FBJ osteosarcoma virus	Mouse	Transcription factor (AP1 component)
<i>jun</i>	Avian sarcoma virus 17	Chicken	Transcription factor (AP1 component)
<i>myb</i>	Avian myeloblastosis virus	Chicken	Transcription factor
<i>myc</i>	MC29 myelocytoma virus	Chicken	Transcription factor (NF- κ B family)

AP1, activator protein 1; **FBJ**, Finkel-Biskis-Jinkins; **GDP**, guanosine diphosphate; **GTP**, guanosine triphosphate; **NF- κ B**, nuclear factor κ B.

Source: Modified from Butel JS. Viral carcinogenesis: revelation of molecular mechanisms and etiology of human disease. *Carcinogenesis*. 2000;21:405. By permission of Oxford University Press.

substantially reduces the incidence of HPV16/18-related cervical precancers and cervical cancer.⁹² The American Cancer Society now recommends routine HPV vaccination principally for females aged 11 to 12 years, but also for females aged 13 to 18 years to “catch up” those who missed the opportunity to be vaccinated or who need to complete the vaccination series.⁹³

CANCER RISK ASSESSMENT

Cancer risk assessment is an important part of the initial evaluation of any patient. A patient’s cancer risk not only is an important determinant of cancer screening recommendations but also may alter how aggressively an indeterminate finding will be pursued for diagnosis. A “probably benign” mammographic lesion, for example, defined as one with <2% probability of malignancy (American College of Radiology category III) is usually managed with a 6-month follow-up mammogram in a patient at baseline cancer risk, but obtaining a tissue diagnosis may be preferable in a patient at high risk for breast cancer.⁹⁴

Cancer risk assessment starts with taking a complete history that includes history of environmental exposures to potential carcinogens and a detailed family history. Risk assessment for breast cancer, for example, includes obtaining a family history to determine whether another member of the family is known to carry a breast cancer susceptibility gene; whether there is familial clustering of breast cancer, ovarian cancer, thyroid cancer, sarcoma, adrenocortical carcinoma, endometrial cancer,

brain tumors, dermatologic manifestations, leukemia, or lymphoma; and whether the patient is from a population at increased risk, such as individuals of Ashkenazi Jewish descent. Patients who have a family history suggestive of a cancer susceptibility syndrome such as hereditary breast-ovarian syndrome, LFS, or CD would benefit from genetic counseling and possibly genetic testing.

There are several models that can estimate risk based on complex family histories and assist clinicians in estimating breast cancer risk or the likelihood that a BRCA mutation is present, including the Claus model, Tyrer-Cuzick model, BRCAPRO model, and the Breast and Ovarian Analysis of Disease Incidence and Carrier Estimation Algorithm (BOADICEA) model.⁹⁵⁻⁹⁸ Patients who do have a strong hereditary component of risk can be evaluated on the basis of their age, race, personal history, and exposures. One of the most commonly used models for risk assessment in breast cancer is the Gail model.⁹⁹ Gail and colleagues analyzed the data from 2852 breast cancer cases and 3146 controls from the Breast Cancer Detection and Demonstration Project, a mammography screening project conducted in the 1970s, and developed a model for projecting breast cancer incidence. The model uses risk factors such as an individual’s age, age at menarche, age at first live birth, number of first-degree relatives with breast cancer, number of previous breast biopsy specimens, and whether the biopsy specimen results revealed atypical ductal hyperplasia (Table 10-8).⁹⁹ This model has led to the development of a

Table 10-8

Assessment of risk for invasive breast cancer

RISK FACTOR	RELATIVE RISK (%)
Age at menarche (years)	
>14	1.00
12–13	1.10
<12	1.21
Age at first live birth (years)	
Patients with no first-degree relatives with cancer	
<20	1.00
20–24	1.24
25–29 or nulliparous	1.55
≥30	1.93
Patients with one first degree-relative with cancer	
<20	1.00
20–24	2.64
25–29 or nulliparous	2.76
≥30	2.83
Patients with ≥2 first-degree relatives with cancer	
<20	6.80
20–24	5.78
25–29 or nulliparous	4.91
≥30	4.17
Breast biopsies (number)	
Patients aged <50 y at counseling	
0	1.00
1	1.70
≥2	2.88
Patients aged ≥50 y at counseling	
0	1.00
1	1.27
≥2	1.62
Atypical hyperplasia	
No biopsies	1.00
At least 1 biopsy, no atypical hyperplasia	0.93
No atypical hyperplasia, hyperplasia status unknown for at least 1 biopsy	1.00
Atypical hyperplasia in at least 1 biopsy	1.82

Source: Modified from Gail MH et al.⁹⁹

breast cancer risk assessment tool, which is available on the World Wide Web.¹⁰⁰ This tool incorporates the risk factors used in the Gail model, as well as race and ethnicity, and allows a health professional to project a woman's individualized estimated risk for invasive breast cancer over a 5-year period

and over her lifetime (to age 90 years). Notably, these risk projections assume that the woman is undergoing regular clinical breast examinations and screening mammograms. Also of note is that this program underestimates the risk for women who have already had a diagnosis of invasive or noninvasive breast cancer and does not take into account specific genetic predispositions such as mutations in *BRCA1* or *BRCA2*. However, risk assessment tools such as this have been validated and are now in widespread clinical use. Similar models are in development or are being validated for other cancers. For example, a lung cancer risk prediction model, which includes age, sex, asbestos exposure history, and smoking history, has been found to predict risk of lung cancer.¹⁰¹ There is now growing interest in using each individual's genotype, such as presence or absence of single nucleotide polymorphisms which each may confer low or intermediate cancer risk. Risk models that include biological as well as environmental factors may accurately predict cancer risk, providing better guidance as to which patients should undergo more intensive screening (e.g., screening with magnetic resonance imaging of the breast, computerized tomography screening of the lung), and should be considered for preventive strategies.

CANCER SCREENING

Early detection is the key to success in cancer therapy. Screening for common cancers using relatively noninvasive tests is expected to lead to early diagnosis, allow more conservative surgical therapies with decreased morbidity, and potentially improve surgical cure rates and overall survival rates. Key factors that influence screening guidelines are how prevalent the cancer is in the population, what risk is associated with the screening measure, and whether early diagnosis actually affects outcome. The value of a widespread screening measure is likely to go up with the prevalence of the cancer in a population, which often determines the age cutoffs for screening and explains why screening is done only for common cancers. The risks associated with the screening measure are a significant consideration, especially with more invasive screening measures such as colonoscopy. The consequences of a false-positive screening test result also need to be considered. For example, when 1000 screening mammograms are taken, only 2 to 4 new cases of cancer will be identified; this number is slightly higher (6 to 10 prevalent cancers per 1000 mammograms) for initial screening mammograms.¹⁰² However, as many as 10% of screening mammograms may be potentially suggestive of an abnormality, which requires further imaging (i.e., a 10% recall rate). Of those women with abnormal mammogram findings, only 5% to 10% will be determined to have a breast cancer. Among women for whom biopsy specimen is recommended, 25% to 40% will have a breast cancer. A false-positive screening result is likely to induce significant emotional distress in patients, leads to unnecessary biopsy specimens, and has cost implications for the health care system.

The 2013 American Cancer Society guidelines for the early detection of cancer are listed in Table 10-9.⁹³ These guidelines are updated periodically to incorporate emerging technologies and new data on the efficacy of screening measures. Besides the American Cancer Society, several other professional bodies make recommendations for screening. Although the screening guidelines differ somewhat, most organizations do not emphasize one screening strategy as superior to another, but all emphasize the importance of age-appropriate screening.

Table 10-9

American Cancer Society recommendations for early detection of cancer in average-risk, asymptomatic individuals

CANCER SITE	POPULATION	TEST OR PROCEDURE	FREQUENCY
Breast	Women, aged ≥ 20 y	BSE	It is acceptable for women to choose not to do BSE or to do BSE regularly (monthly) or irregularly. Beginning in their early 20s, women should be told about the benefits and limitations of BSE. Whether a woman ever performs BSE, the importance of prompt reporting of any new breast symptoms to a health professional should be emphasized. Women who choose to do BSE should receive instruction and have their technique reviewed on the occasion of a periodic health examination.
		CBE	For women in their 20s and 30s, it is recommended that CBE be part of a periodic health examination, preferably at least every 3 y. Asymptomatic women aged ≥ 40 y should continue to receive a CBE as part of a periodic health examination, preferably annually.
		Mammography	Begin annual mammography at age 40 y. ^a
Cervix	Woman, aged 21–65 y	Pap test and HPV DNA test	Cervical cancer screening should begin at age 21 y. For women aged 21–29 y, screening should be done every 3 y with conventional or liquid-based Pap tests. For women aged 30–65 y, screening should be done every 5 y with both the HPV test and the Pap test (preferred), or every 3 y with the Pap test alone (acceptable). Women aged >65 y who have had ≥ 3 consecutive negative Pap tests or ≥ 2 consecutive negative HPV and Pap tests within the last 10 y, with the most recent test occurring within the last 5 y, and women who have had a total hysterectomy should stop cervical cancer screening. Women at any age should not be screened annually by any screening method.
Colorectal	Men and women aged ≥ 50 y	FOBT with at least 50% test sensitivity for cancer, or FIT with at least 50% test sensitivity for cancer, or	Annual, starting at age 50 y. Testing at home with adherence to manufacturer's recommendation for collection techniques and number of samples is recommended. FOBT with the single stool sample collected on the clinician's fingertip during a DRE in the healthcare setting is not recommended. Guaiac-based toilet bowl FOBT tests also are not recommended. In comparison with guaiac-based tests for the detection of occult blood, immunochemical tests are more patient-friendly, and are likely to be equal or better insensitivity and specificity. There is no justification for repeating FOBT in response to an initial positive finding.
		Stool DNA test ^b , or	Interval uncertain, starting at age 50 y.
		FSIG, or	Every 5 y, starting at age 50 y. FSIG can be performed alone, or consideration can be given to combining FSIG performed every 5 y with a highly sensitive guaiac-based FOBT or FIT performed annually.
		DCBE, or	Every 5 y, starting at age 50 y.
		Colonoscopy	Every 10 y, starting at age 50 y.
Endometrial	Women, at menopause	CT colonography	Every 5 yr, starting at age 50 y.
			At the time of menopause, women at average risk should be informed about the risks and symptoms of endometrial cancer and strongly encouraged to report any unexpected bleeding or spotting to their physicians.

Table 10-9

American Cancer Society recommendations for early detection of cancer in average-risk, asymptomatic individuals (continued)

CANCER SITE	POPULATION	TEST OR PROCEDURE	FREQUENCY
Lung	Current or former smokers aged 50–74 in good health with at least a 30 pack-year history	LDCT	Clinicians with access to high-volume, high-quality lung cancer screening and treatment centers should initiate a discussion about lung cancer screening with apparently healthy patients aged 55–74 y who have at least a 30 pack-y smoking history, and who currently smoke or have quit within the past 15 y. A process of informed and shared decision-making with a clinician related to the potential benefits, limitations, and harms associated with screening for lung cancer with LDCT should occur before any decision is made to initiate lung cancer screening. Smoking cessation counseling remains a high priority for clinical attention in discussions with current smokers, who should be informed of their continuing risk of lung cancer. Screening should not be viewed as an alternative to smoking cessation.
Prostate	Men, aged ≥ 50 y	DRE and PSA	Men who have at least a 10-y life expectancy should have an opportunity to make an informed decision with their health care provider about whether to be screened for prostate cancer, after receiving information about the potential benefits, risks, and uncertainties associated with prostate cancer screening. Prostate cancer screening should not occur without an informed decision-making process.
Cancer-related checkup	Men and women aged ≥ 20 y		On the occasion of a periodic health examination, the cancer-related checkup should include examination for cancers of the thyroid, testicles, ovaries, lymph nodes, oral cavity, and skin, as well as health counseling about tobacco, sun exposure, diet and nutrition, risk factors, sexual practices, and environmental and occupational exposures.

ACS, American Cancer Society; BSE, breast self-examination; CBE, clinical breast examination; Pap, Papanicolaou; HPV, human papillomavirus; FOBT, fecal occult blood test; FIT, fecal immunochemical test; DRE, digital rectal examination; FSIG, flexible sigmoidoscopy; DCBE, double-contrast barium enema; CT, computed tomography; LDCT, low-dose helical CT; PSA, prostate-specific antigen.

^aBeginning at age 40 y, annual CBE should ideally be performed prior to mammography.

^bThe stool DNA test approved for colorectal cancer screening in 2008 is no longer commercially available. New stool DNA tests are presently undergoing evaluation and may become available at some future time.

Source: Modified with permission from John Wiley and Sons: Smith RA et al. Cancer screening in the United States, 2013: a review of current American Cancer Society guidelines, current issues in cancer screening, and new guidance on cervical cancer screening and lung cancer screening. CA: a cancer journal for clinicians. 2013;63:87. © 2013 American Cancer Society, Inc.

Screening guidelines are developed for the general baseline-risk population. These guidelines need to be modified for patients who are at high risk. For example, more intensive colorectal cancer screening is recommended for individuals at increased risk because of a history of adenomatous polyps, a personal history of colorectal cancer, a family history of either colorectal cancer or colorectal adenomas diagnosed in a first-degree relative before age 60 years, a personal history of inflammatory bowel disease of significant duration, or a family history or genetic test result indicating FAP or HNPCC. For some diseases, in higher risk populations, both the screening modality and the screening intensity may be altered. For example, breast magnetic resonance imaging is recommended as an adjunct to mammography for breast cancer screening in BRCA mutation carriers, first-degree relatives of carriers, and women with a lifetime breast cancer risk of 20% to 25% or higher.¹⁰³

More recently, the National Lung Screening Trial demonstrated a 20% reduction in lung cancer deaths in adults aged 55 to 74 years who were at high risk of lung cancer and randomized

to low-dose helical computed tomography (LDCT) screening compared with screening with annual CXR.¹⁰⁴ In 2013, the American Cancer Society updated their lung cancer screening recommendations to emphasize that clinicians with access to high-volume, high-quality lung cancer screening and treatment centers should ascertain the smoking history of their patients 55 to 74 years of age, and should discuss lung cancer screening with those who have at least a 30 pack-year smoking history, currently smoke, or have quit within the past 15 years, and who are in relatively good health.¹⁰⁵ It is recommended that this discussion include the benefits, uncertainties, and harms associated with screening for lung cancer with LDCT.

CANCER DIAGNOSIS

The definitive diagnosis of solid tumors is obtained by performing a biopsy specimen of the lesion. Biopsy findings determine the tumor histology and grade and thus, assist in definitive therapeutic planning. Biopsy specimens of mucosal lesions usually are

obtained endoscopically (e.g., via colonoscope, bronchoscope, or cystoscope). Lesions that are easily palpable, such as those of the skin, can either be excised or sampled by punch biopsy specimen. Deep-seated lesions can be localized with computed tomographic (CT) scan or ultrasound guidance for biopsy specimen.

A sample of a lesion can be obtained with a needle or with an open incisional or excisional biopsy specimen. Fine-needle aspiration is easy and relatively safe, but has the disadvantage of not giving information on tissue architecture. For example, fine-needle aspiration biopsy specimen of a breast mass can make the diagnosis of malignancy but cannot differentiate between an invasive and noninvasive tumor. Therefore core-needle biopsy specimen is more advantageous when the histologic findings will affect the recommended therapy. Core biopsy specimen, like fine-needle aspiration, is relatively safe and can be performed either by direct palpation (e.g., a breast mass or a soft tissue mass) or can be guided by an imaging study (e.g., stereotactic core biopsy specimen of the breast). Core biopsy specimens, like fine-needle aspirations, have the disadvantage of introducing sampling error. For example, 19% to 44% of patients with a diagnosis of atypical ductal hyperplasia based on core biopsy specimen findings of a mammographic abnormality are found to have carcinoma upon excision of the lesion.¹⁰⁶ It is crucial to ensure that the histologic findings are consistent with the clinical scenario and to know the appropriate interpretation of each histologic finding. A needle biopsy specimen for which the report is inconsistent with the clinical scenario should be either repeated or followed by an open biopsy specimen.

Open biopsy specimens have the advantage of providing more tissue for histologic evaluation and the disadvantage of being an operative procedure. Incisional biopsy specimens are reserved for very large lesions in which a definitive diagnosis cannot be made by needle biopsy specimen. Excisional biopsy specimens are performed for lesions for which either core biopsy specimen is not possible or the results are nondiagnostic. Excisional biopsy specimens should be performed with curative intent, that is, by obtaining adequate tissue around the lesion to ensure negative surgical margins. Marking of the orientation of the margins by sutures or clips by the surgeon and inking of the specimen margins by the pathologist will allow for determination of the surgical margins and will guide surgical re-excision if one or more of the margins are positive for microscopic tumor or are close. The biopsy specimen incision should be oriented to allow for excision of the biopsy specimen scar if repeat operation is necessary. Furthermore, the biopsy specimen incision should directly overlie the area to be removed rather than tunneling from another site, which runs the risk of contaminating a larger field. Finally, meticulous hemostasis during a biopsy specimen is essential, because a hematoma can lead to contamination of the tissue planes and can make subsequent follow-up with physical examinations much more challenging.

CANCER STAGING

Cancer staging is a system used to describe the anatomic extent of a malignant process in an individual patient. Staging systems may incorporate relevant clinical prognostic factors such as tumor size, location, extent, grade, and dissemination to regional lymph nodes or distant sites. Accurate staging is essential in designing an appropriate treatment regimen for an individual patient. Staging of the lymph node basin is considered a standard part of primary surgical therapy for most surgical procedures and

is discussed later in this chapter. Cancer patients who are considered to be at high risk for distant metastasis usually undergo a preoperative staging work-up. This involves a set of imaging studies of sites of preferential metastasis for a given cancer type. For a patient with breast cancer, for example, a staging work-up would include a chest radiograph, bone scan, and liver ultrasound, or CT scan of the abdomen to evaluate for lung, bone, and liver metastases, respectively. A distant staging work-up usually is performed only for patients likely to have metastasis based on the characteristics of the primary tumor; for example, a staging work-up for a patient with ductal carcinoma in situ of the breast or a small invasive breast tumor is likely to be low yield and not cost effective.

Recently there also is interest in using molecular imaging with positron emission tomography (PET) scanning, or PET/CT, for cancer staging. Most commonly PET scanning is performed with fluorine 18 incorporated into fluorodeoxyglucose (FDG). FDG PET assesses the rate of glycolysis. FDG uptake is increased in most malignant tissues but also in benign pathologic conditions such as inflammatory disorders, trauma, infection, and granulomatous disease. It may be especially useful in the staging and management of lymphoma, lung cancer, and colorectal cancer. The role of PET in evaluating many other cancers is evolving, and additional molecular tracers, such as 3'-deoxy-3'-¹⁸F-fluorothymidine, used to assess proliferation, are being actively pursued.

Standardization of staging systems is essential to allow comparison of results from different studies from different institutions and worldwide. The staging systems proposed by the American Joint Committee on Cancer (AJCC) and the Union Internationale Contre le Cancer (International Union Against Cancer, or UICC) are among the most widely accepted staging systems. Both the AJCC and the UICC have adopted a shared tumor, node, and metastasis (TNM) staging system that defines the cancer in terms of the anatomic extent of disease and is based on assessment of three components: the size of the primary tumor (T), the presence (or absence) and extent of nodal metastases (N), and the presence (or absence) and extent of distant metastases (M).

The TNM staging applies only to tumors that have been microscopically confirmed to be malignant. Standard TNM staging (clinical and pathologic) is completed at initial diagnosis. Clinical staging (cTNM or TNM) is based on information gained up until the initial definitive treatment. Pathologic staging (pTNM) includes clinical information and information obtained from pathologic examination of the resected primary tumor and regional lymph nodes. Other classifications, such as retreatment staging (rTNM) or autopsy staging (aTNM), should be clearly identified as such.

The clinical measurement of tumor size (T) is the one judged to be the most accurate for each individual case based on physical examination and imaging studies. For example, in breast cancer the size of the tumor could be obtained from a physical examination, mammogram, or ultrasound, and the tumor size is based only on the invasive component.

If even one lymph node is involved by tumor, the N component is at least N1. For many solid tumor types, simply the absence or presence of lymph node involvement is recorded, and the tumor is categorized either as N0 or N1. For other tumor types, the number of lymph nodes involved, the size of the lymph nodes or the lymph node metastasis, or the regional lymph node basin involved also has been shown to have prognostic value.

In these cancers, the designations N1, N2, and N3 suggest an increasing abnormality of lymph nodes based on size, characteristics, and location. NX indicates that the lymph nodes cannot be fully assessed.

Cases in which there is no distant metastasis are designated M0, cases in which one or more distant metastases are detected are designated M1, and cases in which the presence of distant metastasis cannot be assessed are designated MX. In clinical practice, negative findings on clinical history and examination are sufficient to designate a case as M0. However, in clinical trials, routine follow-up often are performed to standardize the detection of distant metastases.

The practice of dividing cancer cases into groups according to stage is based on the observation that the survival rates are higher for localized (lower-stage) tumors than for tumors that have extended beyond the organ of origin. Therefore, staging assists in selection of therapy, estimation of prognosis, evaluation of treatments, and exchange of information among treatment centers. Notably, the AJCC regularly updates its staging system to incorporate advances in prognostic technology to improve the predictive accuracy of the TNM system. Therefore it is important to know which revision of a staging system is being used when evaluating studies.

TUMOR MARKERS

Prognostic and Predictive Tissue Markers

Tumor markers are substances that can be detected in higher than normal amounts in the serum, urine, or tissues of patients with certain types of cancer. Tumor markers are produced either by the cancer cells themselves or by the body in a response to the cancer.

Over the past decade, there has been an especially high interest in identifying tissue tumor markers that can be used as prognostic or predictive markers. Although the terms *prognostic marker* and *predictive marker* are sometimes used interchangeably, the term *prognostic marker* generally is used to describe molecular markers that predict disease-free survival, disease-specific survival, and overall survival, whereas the term *predictive marker* often is used in the context of predicting response to certain therapies.

The goal is to identify prognostic markers that can give information on prognosis independent of other clinical characteristics and therefore can provide information to supplement the projections based on clinical presentation. This would allow practitioners to further classify patients as being at higher or lower risk within clinical subgroups and to identify patients who may benefit most from adjuvant therapy. For example, ideal prognostic tumor markers would be able to help determine which patients with node-negative breast cancer are at higher risk of relapse so that adjuvant systemic therapy could be given only to that group. However, although a large number of studies have identified potential novel prognostic markers, most have not been tested with enough vigor to be shown to be of clinical utility. In the 2007 American Society of Clinical Oncology (ASCO) guidelines, it was decided that level of uPA/PAI-1 measured by enzyme-linked immunosorbent assay could be used to determine prognosis in cases of newly diagnosed node-negative breast cancer.¹⁰⁷ In contrast, the data for many other markers, including DNA content, proportion of tumor cells in S phase, Ki-67, cyclin E, p27, p21, thymidine kinase, topoisomerase II, HER2, p53, and cathepsin D, were felt to be insufficient to support their use in the management of breast cancer patients.¹⁰⁷ Similarly, in the 2006 ASCO GI tumor guidelines,

the data were felt to be insufficient to recommend the routine use of p53, *ras*, thymidine synthase, dihydropyrimidine dehydrogenase, thymidine phosphorylase, microsatellite instability, 18q loss of heterozygosity, or deleted-in-colon-cancer protein in the management of patients with colorectal cancer.¹⁰⁸

Predictive markers are markers that can prospectively identify patients who will benefit from a certain therapy. For example in breast cancer, estrogen receptor (ER) and *HER2* assessment can identify patients who can benefit from antiestrogen therapies (e.g., tamoxifen) and anti-*HER2* targeted therapies (e.g., trastuzumab), respectively, and the 2007 ASCO guidelines recommend that these markers be routinely assessed.¹⁰⁷ High-throughput techniques such as transcriptional profiling allow for assessment of the relative mRNA levels of thousands of genes simultaneously in a given tumor using microarray technology. With the advent of such molecular profiling technologies, researchers have focused on identifying expression profiles that are prognostic for different cancer types. For breast cancer, although many such multiparameter tests are under development, few have reached the large-scale validation stage.¹⁰⁹ In 2007, ASCO guidelines suggested that one of these, the *Oncotype DX* assay, can be used to predict recurrence in women with node-negative, ER-positive breast cancer who are treated with tamoxifen.¹⁰⁷ *Oncotype DX* is a quantitative reverse-transcriptase polymerase chain reaction (RT-PCR) test that used paraffin-fixed tissue. A 21-gene recurrence score (RS) is generated based on the expression of 16 cancer genes and 5 reference genes. The levels of expression are used to derive an RS that ranges from 0 to 100, using a prospectively defined mathematical algorithm. This novel quantitative approach to the evaluation of the best-known molecular pathways in breast cancer has produced impressive results. Use of this multigene assay to predict recurrence was validated in the National Surgical Adjuvant Breast and Bowel Project (NSABP) B-14 trial, in which ER-positive, node-negative patients had received tamoxifen.¹¹⁰ By multivariate Cox proportional analysis, RS was found to be independently associated with recurrence risk, with a hazard ratio of 3.21 (95% confidence interval of 2.23 to 4.65, $P < .001$). The RS was indeed able to stratify patients by freedom from distant recurrence (Fig. 10-13).¹¹⁰ The Trial Assessing Individualized

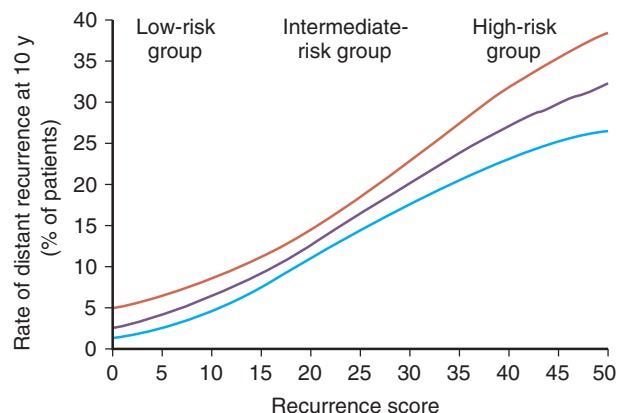


Figure 10-13. Distant recurrence as a continuous function of the recurrence score derived from tumor levels of expression of 21 genes. (From Paik S, et al: A multigene assay to predict recurrence of tamoxifen-treated, node-negative breast cancer. *N Engl J Med*. 2004;351:281. Copyright © 2004 Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society.)¹¹⁰

Options for Treatment for breast cancer (TAILORx) is evaluating the utility of Oncotype DX for predicting prognosis in patients with ER-positive, node-negative tumors and will focus on women with intermediate RS scores in whom the role of chemotherapy is unclear. Several other multigene predictors for breast cancer are available including MammaPrint, a gene expression profiling platform assessing a 70-gene transcriptional signature.¹¹¹ This assay was approved by the Food and Drug Administration (FDA) in February 2007. The usefulness of this assay in making therapy-related decisions is being tested prospectively in a large-scale study, the Microarray in Node-Negative Disease May Avoid Chemotherapy (MINDACT) trial.

Multigene profiles to predict prognosis are in development or in validation phases for many other solid tumor types, including lung cancer, ovarian cancer, pancreatic cancer, colorectal cancer, and melanoma. Gene signatures and genomic alterations also are being studied for their ability to predict response to specific chemotherapy regimens or targeted therapies. Many of these multigene marker sets will likely be incorporated into clinical practice in the years to come.

Serum Markers

Serum markers are under active investigation because they may allow early diagnosis of a new cancer or may be used to follow cancer response to therapy or monitor for recurrence. Unfortunately, identification of serum markers of clinical value has been challenging. Many of the tumor markers proposed so far have had low sensitivities and specificities.¹⁰⁹ Tumor marker levels may not be elevated in all patients with cancer, especially in the early stages, when a serum marker would be most useful for diagnosis. Therefore when a tumor marker is used to monitor recurrence, it is important to be certain that the level of the tumor marker was elevated before primary therapy. Moreover, tumor marker levels can be elevated in benign conditions. Many tumor markers are not specific for a certain type of cancer and can be elevated with more than one type of tumor. Since there may be significant laboratory variability, it is important to obtain serial results from the same laboratory. In spite of these many clinical limitations, several serum markers are in clinical use. A few of the commonly measured serum tumor markers are discussed in the following sections.

Prostate-Specific Antigen. Prostate-specific antigen (PSA) is an androgen-regulated serine protease produced by the prostate epithelium. PSA is normally present in low concentrations in the blood of all adult males. PSA levels may be elevated in the blood of men with benign prostate conditions such as prostatitis and benign prostatic hyperplasia, as well as in men with prostate cancer. PSA levels have been shown to be useful in evaluating the effectiveness of prostate cancer treatment and monitoring for recurrence after therapy. In monitoring for recurrence, a trend of increasing levels is considered more significant than a single absolute elevated value.

Although PSA has been widely used for prostate cancer screening, the utility of PSA screening remains controversial. There is concern that the number of men who avoid dying from prostate cancer due to screening is small, while the harms related to the treatment of screen-detected cancers, including incontinence and erectile dysfunction are at least moderate. In 2012, the US Preventive Services Task Force concluded with moderate certainty that the harms of PSA testing outweigh the benefits and on that basis recommended against PSA-based screening

for all men.¹¹² In 2010, the American Cancer Society updated its guidelines for the early detection of prostate cancer to state that men who have at least a 10-year life expectancy should have an opportunity to make an informed decision with their health care provider about whether to be screened for prostate cancer with digital rectal exam and serum PSA, after receiving information about the benefits, risks, and uncertainties associated with prostate cancer screening;¹¹³ this recommendation was reinforced in their 2013 guidelines.⁹³

Carcinoembryonic Antigen. Carcinoembryonic antigen (CEA) is a glycoprotein found in the embryonic endodermal epithelium. Elevated CEA levels have been detected in patients with primary colorectal cancer as well as in patients with breast, lung, ovarian, prostate, liver, and pancreatic cancer. Levels of CEA also may be elevated in benign conditions, including diverticulitis, peptic ulcer disease, bronchitis, liver abscess, and alcoholic cirrhosis, especially in smokers and in elderly persons.

CEA measurement is most commonly used in the management of colorectal cancer. However, the appropriate use of CEA testing in patients with colorectal cancer has been debated. Use of CEA level as a screening test for colorectal cancer is not recommended. CEA levels may be useful if obtained preoperatively and postoperatively in patients with a diagnosis of colorectal cancer. Preoperative elevation of CEA level is an indicator of poor prognosis. However, the 2007 ASCO clinical practice guidelines state that the data are insufficient to support the use of CEA to determine whether to give a patient adjuvant therapy; the data are stronger for the use of CEA for monitoring for postoperative recurrence.¹⁰⁷ CEA measurement is the most cost-effective approach for detecting metastasis, with 64% of recurrences being detected first by an elevation in CEA level. Therefore, in cases in which the patient would be a candidate for resection of recurrent colorectal cancer or systemic therapy, the 2006 ASCO guidelines recommend that postoperative CEA testing be performed every 3 months in patients with stage II or III disease for at least 3 years.¹⁰⁸ CEA is the marker of choice for monitoring metastatic colorectal cancer during systemic therapy.¹⁰⁸

There is also interest in using CEA levels for monitoring patients with breast cancer. However, the 2007 ASCO guidelines state that the routine use of CEA for screening, diagnosis, staging, or surveillance of breast cancer is not recommended because available data are insufficient.¹⁰⁷ For monitoring patients during active therapy, CEA can be used in conjunction with diagnostic imaging and history and physical examination.¹⁰⁷ In the absence of measurable disease, an increase in CEA level may be taken to indicate treatment failure. However, caution is advised when interpreting rising levels in the first 4 to 6 weeks of therapy.¹⁰⁷

Alpha-Fetoprotein. Alpha-fetoprotein (AFP) is a glycoprotein normally produced by a developing fetus. AFP levels decrease soon after birth in healthy adults. An elevated level of AFP suggests the presence of either primary liver cancer or a germ cell tumor of the ovary or testicle. Rarely, other types of cancer such as gastric are associated with an elevated AFP level. Benign conditions that can cause elevations of AFP include cirrhosis, hepatic necrosis, acute hepatitis, chronic active hepatitis, ataxia-telangiectasia, Wiskott-Aldrich syndrome, and pregnancy.¹¹⁴

The sensitivity of an elevated AFP level for detecting HCC is approximately 60%. AFP is considered to be sensitive

and specific enough to be used for screening for HCC in high-risk populations. Current consensus recommendations are to screen healthy hepatitis B virus carriers with annual or semi-annual measurement of AFP level and to screen carriers with cirrhosis or chronic hepatitis and patients with cirrhosis of any etiology with twice-yearly measurement of AFP level and liver ultrasonography.¹¹⁵ Although AFP testing has been used widely for a long time, its efficacy in early diagnosis of HCC is limited. With improvements in imaging technology, a larger proportion of patients diagnosed with HCC are now AFP seronegative.

Cancer Antigen 19-9. Cancer antigen 19-9 (CA 19-9) is a tumor-related antigen that was originally defined by a monoclonal antibody produced by a hybridoma prepared from murine spleen cells immunized with a human colorectal cancer cell line.¹⁰⁸ The data are insufficient to recommend use of CA 19-9 for screening, diagnosis, surveillance, or monitoring of therapy for colon cancer.¹⁰⁸ Based on the 2006 ASCO guidelines, there are also insufficient data to recommend use of CA 19-9 for screening, diagnosis, or determination of the operability of pancreatic cancer.¹⁰⁸ However, for patients with locally advanced or metastatic cancer receiving active therapy, CA 19-9 can be measured at the start of therapy and every 1 to 3 months while therapy is given; elevations in serial CA 19-9 levels may indicate progressive disease and should be confirmed by additional studies.¹⁰⁸

Cancer Antigen 15-3. Cancer antigen 15-3 (CA 15-3) is an epitope of a large membrane glycoprotein encoded by the *MUC1* gene that tumor cells shed into the bloodstream. The CA 15-3 epitope is recognized by two monoclonal antibodies in a sandwich radioimmunoassay. CA 15-3 levels are most useful in following the course of treatment in women diagnosed with advanced breast cancer. CA 15-3 levels are infrequently elevated in early-stage breast cancer. CA 15-3 levels can be increased in benign conditions such as chronic hepatitis, tuberculosis, sarcoidosis, pelvic inflammatory disease, endometriosis, systemic lupus erythematosus, pregnancy, and lactation, and in other types of cancer such as lung, ovarian, endometrial, and GI cancers.

The sensitivity of CA 15-3 is higher for metastatic disease, and in these cases studies have shown sensitivity to be between 54% and 87%, with specificity as high as 96%. This has led to interest in using CA 15-3 for monitoring patients with advanced breast cancer for recurrence. Elevated CA 15-3 levels have been reported before relapse in 54% of patients, with a lead time of 4.2 months. Therefore, detection of elevated CA 15-3 levels during follow-up should prompt evaluation for recurrent disease. However, 6% to 8% of patients without recurrence will have elevated CA 15-3 levels that require evaluation. Furthermore, monitoring with the use of CA 15-3 levels has shown no demonstrated impact on survival. Therefore, the 2007 ASCO guidelines state that the routine use of CA 15-3 for screening, diagnosis, staging, or surveillance of breast cancer is not recommended because available data are insufficient.¹⁰⁷ For monitoring patients during active therapy, CA 15-3 can be used in conjunction with diagnostic imaging and history and physical examination.¹⁰⁷ In the absence of measurable disease, an increase may be interpreted to indicate treatment failure. However, caution is advised when interpreting rising levels in the first 4 to 6 weeks of therapy.¹⁰⁷

Cancer Antigen 27-29. The MUC-1 gene product in the serum may be quantitated by using radioimmunoassay with a monoclonal antibody against the cancer antigen 27-29 (CA 27-29). CA 27-29 levels can be elevated in breast cancer as well

as in cancers of the colon, stomach, kidney, lung, ovary, pancreas, uterus, and liver. First-trimester pregnancy, endometriosis, benign breast disease, kidney disease, and liver disease also may be associated with elevated CA 27-29 levels.

CA 27-29 has been reported to have a sensitivity of 57%, a specificity of 98%, a positive predictive value of 83%, and a negative predictive value of 93% in detecting breast cancer recurrences.¹¹⁶ Although CA 27-29 has been found to predict recurrence an average of 5.3 months before other symptoms or tests, testing of CA 27-29 levels has not been demonstrated to affect disease-free and overall survival rates.^{116, 117} Therefore, the 2007 ASCO guidelines state that, as with CA 15-3, the routine use of CA 27-29 for screening, diagnosis, staging, or surveillance of breast cancer is not recommended because available data are insufficient.¹⁰⁷ CA 27-29 levels can be used together with diagnostic imaging and history and physical examination to monitor patients during active therapy.¹⁰⁷ When no measurable disease is present, an increase in level may be considered to indicate treatment failure. However, rising levels in the first 4 to 6 weeks of therapy should be interpreted with caution.¹⁰⁷

Circulating Tumor Cells

Circulating tumor cells (CTCs) are cells present in the blood that possess antigenic or genetic characteristics of a specific tumor type.¹⁰⁷ One CTC detection methodology is capture and quantitation of CTCs with immunomagnetic beads coated with antibody specific for cell-surface, epithelial, or cancer antigens. Another methodology used to detect cancer cells in the peripheral blood is RT-PCR. It has been suggested that measurement of CTCs can be an effective tool for selecting patients who have a high risk of relapse and for monitoring efficacy of cancer therapy.

CTCs have probably been most extensively studied in breast cancer.¹⁰⁷ The most promising data come from the use of CTC measures in metastatic breast cancer. In a prospective multicenter trial, the number of CTCs (≥ 5 CTCs vs. < 5 CTCs per 7.5 mL of whole blood) before treatment of metastatic breast cancer was an independent predictor of progression-free and overall survival rates.¹¹⁸ The presence of > 5 CTCs after the first course of therapy predicted lack of response to treatment. This technology, known as *CellSearch*, has been approved by the FDA for clinical use. Further, in a recent single institutional study, detection of one or more CTCs in Stage I-III breast cancer patients was associated with both decreased progression-free survival and overall survival.¹¹⁹

However, there is limited data to prove that the use of CTC testing leads to improved survival or improved quality of life; thus the ASCO 2007 guidelines update did not recommend the use of CTC measurement in any clinical setting.¹⁰⁷ The clinical utility of measuring CTC response to initial therapy is now being tested prospectively in a multicenter clinical trial. The use of CTC levels as a tool in treating many other types of tumor is also under active investigation.

The prognostic implications of detection of CTCs by RT-PCR have been intensively studied for melanoma. In the recent multicenter Sunbelt Melanoma Trial, serial RT-PCR was performed on peripheral blood samples using four markers—tyrosinase, melanoma antigen reacting to T cell (MART-1), melanoma antigen 3 (MAGE3), and gp 100—to detect occult melanoma cells in the bloodstream.¹²⁰ Although there were no differences in survival between patients in whom at least one marker was detected and those in whom no markers were

detected, the disease-free survival and distant disease-free survival were worse for patients in whom more than one marker was detected at any time during follow-up.¹²⁰ The detection of occult cancer cells with RT-PCR remains investigational, however, and is not used to direct therapy for melanoma and other cancer types at this time.

Bone Marrow Micrometastases

Micrometastatic disease in the bone marrow, also referred to as *minimal residual disease*, also is being investigated as a potential prognostic marker. Bone marrow micrometastatic disease usually is detected by staining bone marrow aspirates with monoclonal antibodies to cytokeratin, but other methodologies such as flow cytometry and RT-PCR are being explored. Breast cancer patients with bone marrow micrometastasis have larger tumors, tumors with a higher histologic grade, more lymph node metastases, and more hormone receptor-negative tumors than patients without bone marrow micrometastasis. In 4700 patients with stage I, II, or III breast cancer, micrometastasis was a significant prognostic factor associated with poor overall survival, breast cancer-specific survival, disease-free survival, and distant disease-free survival during a 10-year observation period.¹²¹ Recently, in the American College of Surgeons Oncology Group Z0010 trial enrolled women with clinical T1 to T2N0M0 invasive breast carcinoma in a prospective observational study to determine to determine the association between survival and metastases detected by immunochemical staining of bone marrow specimens from patients with early-stage breast cancer.¹²² Of 3413 bone marrow specimens examined by immunocytochemistry, only 104 (3.0%) were positive for tumor. Bone marrow involvement was associated with a decreased overall survival but this association was not significant on multivariable analysis. The prognostic implication of bone marrow involvement is also being studied by the National Surgical Adjuvant Breast and Bowel Project Protocol BP-59.

At this time the routine use of bone marrow testing is not recommended.¹⁰⁷ Ongoing clinical trials are evaluating the role of routine assessment of bone marrow status in the care of patients with early and advanced breast cancer. The utility of assessment of bone marrow micrometastasis is also being evaluated in other tumor types, including gastric, esophageal, colorectal, lung, cervical, and ovarian cancer.¹²³

SURGICAL APPROACHES TO CANCER THERAPY

Multidisciplinary Approach to Cancer

Although surgery is an effective therapy for most solid tumors, patients who die from cancer usually die of metastatic disease. Therefore, to improve patient survival rates, a multimodality approach, including systemic therapy and radiation therapy is key for most tumors. It is important that surgeons involved in cancer care not only know the techniques for performing a cancer operation but also know the alternatives to surgery and be well versed in reconstructive options. It is also crucial that the surgeon be familiar with the indications for and complications of preoperative and postoperative chemotherapy and radiation therapy. Although the surgeon may not be delivering these other therapies, as the first physician to see a patient with a cancer diagnosis, he or she is ultimately responsible for initiating the appropriate consultations. For this reason, the surgeon often is responsible for determining the most appropriate adjuvant

therapy for a given patient as well as the best sequence for therapy. In most instances, a multidisciplinary approach beginning at the patient's initial presentation is likely to yield the best result.

Surgical Management of Primary Tumors

The goal of surgical therapy for cancer is to achieve oncologic cure. A curative operation presupposes that the tumor is confined to the organ of origin or to the organ and the regional lymph node basin. Patients in whom the primary tumor is not resectable with negative surgical margins are considered to have inoperable disease. The operability of primary tumors is best determined before surgery with appropriate imaging studies that can define the extent of local-regional disease. For example, a preoperative thin-section CT scan is obtained to determine resectability of pancreatic cancer, which is based on the absence of extrapancreatic disease, the absence of tumor extension to the superior mesenteric artery and celiac axis, and a patent superior mesenteric vein-portal vein confluence.¹²⁴ Disease involving multiple distant metastases is deemed inoperable because it is usually not curable with surgery of the primary tumor. Therefore patients who are at high risk of having distant metastasis should undergo a staging work-up before surgery for the primary tumor. On occasion, primary tumors are resected in these patients for palliative reasons, such as improving the quality of life by alleviating pain, infection, or bleeding. An example of this is toilet mastectomies for large ulcerated breast tumors. Patients with limited metastases from a primary tumor on occasion are considered surgical candidates if the natural history of isolated distant metastases for that cancer type is favorable or the potential complications associated with leaving the primary tumor intact are significant.

In the past it was presumed that the more radical the surgery, the better the oncologic outcome would be. Over the past three decades, this has been recognized as not necessarily being true, which has led to more conservative operations, with wide local excisions replacing compartmental resections of sarcomas, and partial mastectomies, skin-sparing mastectomies, and breast-conserving therapies replacing radical mastectomies for breast cancer. The uniform goal for all successful oncologic operations seems to be achieving widely negative margins with no evidence of macroscopic or microscopic tumor at the surgical margins. The importance of negative surgical margins for local tumor control and/or survival has been documented for many tumor types, including sarcoma, breast cancer, pancreatic cancer, and rectal cancer. Thus it is clear that every effort should be made to achieve microscopically negative surgical margins. Inking of the margins, orientation of the specimen by the surgeon, and immediate gross evaluation of the margins by a pathologist using frozen-section analysis when necessary may assist in achieving negative margins at the first operation. In the end, although radiation therapy and systemic therapy can assist in decreasing local recurrence rates in the setting of positive margins, adjuvant therapy cannot substitute for adequate surgery.

Although it is clear that the surgical gold standard is negative surgical margins, the appropriate surgical margins for optimal local control are controversial for many cancer types. In contrast, in melanoma the optimal margin width for any tumor depth has been better defined, owing to the systematic study of this question in randomized clinical trials.^{125, 126} Although such randomized studies may not be possible for all tumor types, it

is important to determine optimum surgical margins for each cancer type so that adjuvant radiation and systemic therapy can be offered to patients deemed to be at increased risk for local treatment failure. There are also ongoing studies on approaches to assess margins intraoperatively, to allow immediate intraoperative reexcisions as needed, and maximizing local control.

Surgical Management of the Regional Lymph Node Basin

Most neoplasms have the ability to metastasize via the lymphatics. Therefore, most oncologic operations have been designed to remove the primary tumor and draining lymphatics en bloc. This type of operative approach usually is undertaken when the lymph nodes draining the primary tumor site lie adjacent to the tumor bed, as is the case for colorectal cancers and gastric cancers. For tumors in which the regional lymph node basin is not immediately adjacent to the tumor (e.g., melanomas), lymph node surgery can be performed through a separate incision. Unlike most carcinomas, soft tissue sarcomas rarely metastasize to the lymph nodes (<5%); therefore lymph node surgery usually is not necessary.

It is generally accepted that a formal lymphadenectomy is likely to minimize the risk of regional recurrence of most cancers. For example, the introduction of total mesorectal excision of rectal cancer has been associated with a large decline in local-regional recurrence, and this procedure has become the new standard of operative management.¹²⁷ On the other hand, there have been two opposing views regarding the role of lymphadenectomy in survival of cancer patients. The traditional Halsted view states that lymphadenectomy is important for staging and survival. The opposing view counters that cancer is systemic at inception and that lymphadenectomy, although useful for staging, does not affect survival. For most cancers, involvement of the lymph nodes is one of the most significant prognostic factors. Interestingly, in some studies removal of a larger number of lymph nodes has been found to be associated with an improved overall survival rate for many tumors, including breast cancer, colon cancer, and lung cancer. Although this seems to support the Halsted theory that more extensive lymphadenectomy yielding of nodes reduces the risk of regional recurrence, there may be alternative explanations for the same finding. For example, the surgeon who performs a more extensive lymphadenectomy may obtain wider margins around the tumor or even provide

better overall care, such as ensuring that patients receive the appropriate adjuvant therapy or undergo a more thorough staging work-up. Alternatively, the pathologist may perform a more thorough examination, identifying more nodes and more accurately staging the nodes. The effect of appropriate staging on survival is twofold. Patients with nodal metastases may be offered adjuvant therapy, which improves their survival chances. Further, the improved staging can improve perceived survival rates through a “Will Rogers effect”; that is, identification of metastases that had formerly been silent and unidentified leads to stage migration and thus to a perceived improvement in chances of survival. Clearly the impact of lymphadenectomy on survival will not be easily resolved.

Surgical management of the clinically negative regional lymph node basin has evolved with the introduction of lymphatic mapping technology (Fig. 10-14).¹²⁸ Lymphatic mapping and sentinel lymph node biopsy specimen were first reported in 1977 by Cabanas for penile cancer.¹²⁹ Now, sentinel node biopsy specimen is the standard of care for the management of melanoma and breast cancer. Moreover, the utility of sentinel node biopsy specimen in other cancer types is being explored.

The first node to receive drainage from the tumor site is termed the sentinel node. This node is the node most likely to contain metastases, if metastases to that regional lymph node basin are present. The goal of lymphatic mapping and sentinel lymph node biopsy specimen is to identify and remove the lymph node most likely to contain metastases in the least invasive fashion. The practice of sentinel lymph node biopsy specimen followed by regional lymph node dissection for selected patients with a positive sentinel lymph node avoids the morbidity of lymph node dissections in patients with negative nodes. An additional advantage of the sentinel lymph node technique is that it directs attention to a single node, which allows more careful analysis of the lymph node most likely to have a positive yield and increases the accuracy of nodal staging. Two criteria are used to assess the efficacy of a sentinel lymph node biopsy specimen: the sentinel lymph node identification rate and the false-negative rate. The sentinel lymph node identification rate is the proportion of patients in whom a sentinel lymph node was identified and removed among all patients undergoing an attempted sentinel lymph node biopsy specimen. The false-negative rate is the proportion of patients with regional lymph node metastases in whom the sentinel lymph node was found

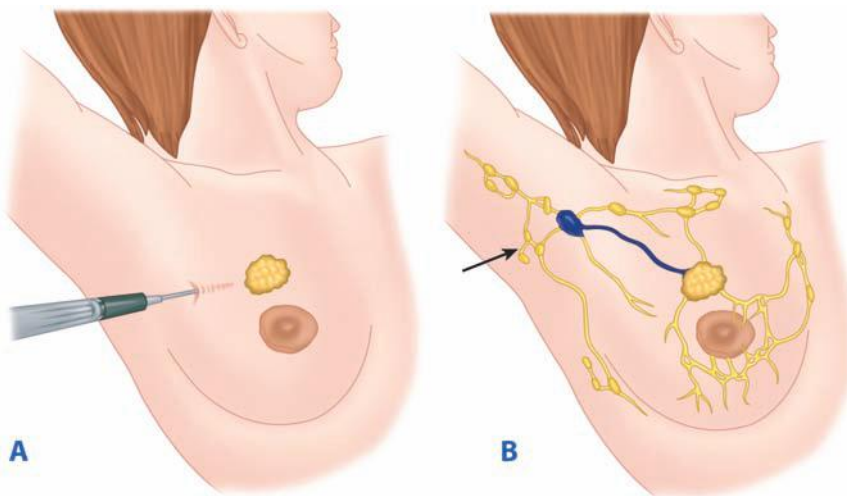


Figure 10-14. Lymphatic mapping and sentinel lymph node biopsy specimen for breast cancer. **A.** Peritumoral injection of blue dye. **B.** Blue dye draining into the sentinel lymph node. (Modified with permission from Meric F, Hunt KK. With kind permission from Springer Science and Business Media.)¹²⁸

to be negative. False-negative biopsy specimen results may be due to identifying the wrong node or to missing the sentinel node (i.e., surgical error) or they may be due to the cancer cells' establishing metastases not in the first node encountered but in a second-echelon node (i.e., biologic variation). Alternatively, false-negative biopsy specimen results may be due to inadequate histologic evaluation of the lymph node. The false-negative rates for sentinel lymph node biopsy specimen in study series range between 0% and 11%. Both increases in the identification rate and decreases in the false-negative rate have been observed as surgeons gain experience with the technique.

Lymphatic mapping is performed by using isosulfan blue dye, technetium-labeled sulfur colloid or albumin, or a combination of both techniques to detect sentinel nodes. The combination of blue dye and technetium has been reported to improve the capability of detecting sentinel lymph nodes. The nodal drainage pattern usually is determined with a preoperative lymphoscintigram, and the "hot" and/or blue nodes are identified with the assistance of a gamma probe and careful nodal basin exploration. Careful manual palpation is a crucial part of the procedure to minimize the false-negative rate.

The nodes are evaluated with serial sectioning, hematoxylin and eosin staining, and immunohistochemical analysis with S-100 protein and homatropine methylbromide staining for melanoma and cytokeratin staining for breast cancer. The utility of molecular techniques such as RT-PCR to assess the sentinel nodes is still being explored.

Another area of active investigation is the prognostic value of minimal nodal involvement. For example, in breast cancer, nodes with isolated tumor cell deposits of <0.2 mm (also called *nanometastasis*) are considered to be N0 by the sixth edition of the AJCC staging manual. However, some retrospective studies have suggested that even this amount of nodal disease burden has negative prognostic implications.¹³⁰ Molecular ultrastaging with RT-PCR for patients with node-negative disease was assessed in a prospective multicenter trial and was found not to be prognostic in malignant melanoma.¹²⁰ However, a recent meta-analysis of 22 studies enrolling 4019 patients found that PCR positivity was associated with worse overall and disease-free survival.¹³¹ Further study of the utility of ultrastaging of nodes in breast cancer, melanoma, and several other tumor types is ongoing.

Until recently, in breast cancer management, when sentinel node mapping revealed a positive sentinel node, this was followed by a completion axillary lymph node dissection. Recently results of the American College of Surgeons Oncology Group Z0011 trial, challenged this practice. ACOSOG Z11 was a phase 3 multicenter noninferiority trial conducted to determine the effects of complete axillary lymph node dissection on survival of patients with sentinel lymph node metastasis of breast cancer.¹²² Patients were women with clinical T1-T2 invasive breast cancer, no palpable adenopathy, and 1 to 2 SLNs containing metastases identified by frozen section, touch preparation, or hematoxylin-eosin staining on permanent section. All patients underwent breast-conserving surgery and tangential whole-breast irradiation. Those with sentinel node metastases identified by sentinel node biopsy specimen were randomized to undergo axillary lymph node dissection or no further axillary treatment. At a median follow-up of 6.3 years, 5-year overall survival was 91.8% (95% confidence interval [CI], 89.1%–94.5%) with axillary lymph node dissection and 92.5% (95% CI, 90.0%–95.1%) with sentinel node alone. The 5-year disease-free survival was 82.2% (95% CI, 78.3%–86.3%) with

axillary lymph node dissection, and 83.9% (95% CI, 80.2%–87.9%) with sentinel node alone. Thus ACOSOG Z11 demonstrated that among breast cancer patients with limited sentinel node metastasis treated with breast conservation and systemic therapy, the use of sentinel node alone compared with axillary lymph node dissection did not result in inferior survival. This study challenges the traditional surgical dictum of regional management, and has led to a selective utilization of completion axillary lymph node dissection in breast cancer patients undergoing breast conservation. The role of completion lymph node dissections in melanoma is under investigation.

Surgical Management of Distant Metastases

The treatment of a patient with distant metastases depends on the number and sites of metastases, the cancer type, the rate of tumor growth, the previous treatments delivered and the responses to these treatments, and the patient's age, physical condition, and desires. Although once a tumor has metastasized it usually is not curable with surgical therapy, such therapy has resulted in cure in selected cases with isolated metastases to the liver, lung, or brain.

Patient selection is the key to the success of surgical therapy for distant metastases. The cancer type is a major determinant in surgical decision making. A liver metastasis from a colon cancer is more likely to be an isolated and thus resectable lesion than a liver metastasis from a pancreatic carcinoma. The growth rate of the tumor also plays an important role and can be determined in part by the disease-free interval and the time between treatment of the primary tumor and detection of the distant recurrence. Patients with longer disease-free intervals have a higher survival rate after surgical metastasectomy than those with a short disease-free interval. Similarly, patients who have synchronous metastases (metastases diagnosed at the initial cancer diagnosis) do worse after metastasectomy than patients who develop metachronous metastases (metastasis diagnosed after a disease-free interval). The natural history of metastatic disease is so poor for some tumors (e.g., pancreatic cancer) that there is no role at this time for surgical metastasectomy. In cancers with a more favorable outlook, observation for several weeks or months, potentially with initial treatment with systemic therapy, can allow the surgeon to monitor for metastases at other sites.

In curative surgery for distant metastases, as with surgery for primary tumors, the goal is to resect the metastases with negative margins. In patients with hepatic metastases that are unresectable because their location near intrahepatic blood vessels precludes a margin-negative resection, or because they are multifocal or hepatic function is inadequate, tumor ablation with cryotherapy or radiofrequency ablation is an alternative.^{132, 133} Curative resections or ablative procedures should be attempted only if the lesions are accessible and the procedure can be performed safely.

CHEMOTHERAPY

Clinical Use of Chemotherapy

In patients with documented distant metastatic disease, chemotherapy is usually the primary modality of therapy. The goal of therapy in this setting is to decrease the tumor burden, thus prolonging survival. It is rare to achieve cure with chemotherapy for metastatic disease for most solid tumors. Chemotherapy administered to a patient who is at high risk for distant recurrence but has no evidence of distant disease is referred to as

adjuvant chemotherapy. The goal of adjuvant chemotherapy is eradication of micrometastatic disease, with the intent of decreasing relapse rates and improving survival rates.

Adjuvant therapy can be administered after surgery (postoperative chemotherapy) or before surgery (preoperative chemotherapy, neoadjuvant chemotherapy, or induction therapy). A portion or all of the planned adjuvant chemotherapy can be administered before the surgical removal of the primary tumor. Preoperative chemotherapy has three potential advantages. The first is that preoperative regression of tumor can facilitate resection of tumors that were initially inoperable or allow more conservative surgery for patients whose cancer was operable to begin with. In the NSABP B-18 project, for example, women were randomly assigned to receive adjuvant doxorubicin and cyclophosphamide preoperatively or postoperatively. More patients treated before surgery than after surgery underwent breast-conserving surgery (68% vs. 60%).¹³⁴ The second advantage of preoperative chemotherapy is the treatment of micrometastases without the delay of postoperative recovery. The third advantage is the ability to assess a cancer's response to treatment clinically, after a number of courses of chemotherapy, and pathologically, after surgical resection. This is especially important if alternative treatment regimens are available to be offered to patients whose disease responded inadequately. Molecular characterization of the residual disease may also give insight into mechanisms of chemoresistance and possible therapeutic targets.

There are some potential disadvantages to preoperative chemotherapy, however. Although disease progression while the patient is receiving preoperative chemotherapy is rare in chemotherapy-sensitive tumors such as breast cancer, it is more frequent in relatively chemotherapy-resistant tumors such as sarcomas.¹³⁵ Thus, patient selection is critical to ensure that the opportunity to treat disease surgically is not lost by giving preoperative chemotherapy. Often, rates of postoperative wound infection, flap necrosis, and delays in postoperative adjuvant therapy do not differ between patients who are treated with preoperative chemotherapy and patients who are treated with surgery first. However, preoperative chemotherapy can introduce special challenges to tumor localization, margin analysis, lymphatic mapping, and pathologic staging.

Response to chemotherapy is monitored clinically with imaging studies as well as physical examinations. Response usually is defined as complete response, partial response, stable disease, or progression. Response generally is assessed using the Response Evaluation Criteria in Solid Tumors (RECIST) criteria.¹³⁶ Objective tumor response assessment is critical, because tumor response is used as a prospective endpoint in clinical trials and tumor response is a guide to clinicians regarding continuation of current therapy.

Principles of Chemotherapy

Chemotherapy destroys cells by first-order kinetics, which means that with the administration of a drug a constant percentage of cells is killed, not a constant number of cells. If a patient with 10^{12} tumor cells is treated with a dose that results in 99.9% cell kill (3-log cell kill), the tumor burden will be reduced from 10^{12} to 10^9 cells (or 1 kg to 1 g). If the patient is re-treated with the same drug, which theoretically could result in another 3-log cell kill, the cells would decrease in number from 10^9 to 10^6 (1 g to 1 mg) rather than being eliminated totally.

Chemotherapeutic agents can be classified according to the phase of the cell cycle during which they are effective.

Cell-cycle phase-nonspecific agents (e.g., alkylating agents) have a linear dose-response curve, such that the fraction of cells killed increases with the dose of the drug.¹³⁷ In contrast, the cell-cycle phase-specific drugs have a plateau with respect to cell killing ability, and cell kill will not increase with further increases in drug dose.

Anticancer Agents

Alkylating Agents. Alkylating agents are cell-cycle-nonspecific agents, that is, they are able to kill cells in any phase of the cell cycle. They act by cross-linking the two strands of the DNA helix or by causing other direct damage to the DNA. The damage to the DNA prevents cell division and, if severe enough, leads to apoptosis. The alkylating agents are composed of three main subgroups: classic alkylators, nitrosoureas, and miscellaneous DNA-binding agents (Table 10-10).

Antitumor Antibiotics. Antitumor antibiotics are the products of fermentation of microbial organisms. Like the alkylating agents, these agents are cell-cycle nonspecific. Antitumor antibiotics damage the cell by interfering with DNA or RNA synthesis, although the exact mechanism of action may differ by agent.

Antimetabolites. Antimetabolites are generally cell-cycle-specific agents that have their major activity during the S phase of the cell cycle and have little effect on cells in G_0 . These drugs are most effective, therefore, in tumors that have a high growth fraction. Antimetabolites are structural analogues of naturally occurring metabolites involved in DNA and RNA synthesis. Therefore, they interfere with normal synthesis of nucleic acids by substituting for purines or pyrimidines in the metabolic pathway to inhibit critical enzymes in nucleic acid synthesis. The antimetabolites include folate antagonists, purine antagonists, and pyrimidine antagonists.

Plant Alkaloids. Plant alkaloids are derived from plants such as the periwinkle plant, *Vinca rosea* (e.g., vincristine, a vinca alkaloid), or the root of American mandrake, *Podophyllum peltatum* (e.g., etoposide, a podophyllotoxin).¹³⁷ Vinca alkaloids affect the cell by binding to tubulin in the S phase. This blocks microtubule polymerization, which results in impaired mitotic spindle formation in the M phase. Taxanes such as paclitaxel, on the other hand, cause excess polymerization and stability of microtubules, which blocks the cell cycle in mitosis. The epipodophyllotoxins act to inhibit a DNA enzyme called *topoisomerase II* by stabilizing the DNA-topoisomerase II complex. This results in an inability to synthesize DNA, and thus the cell cycle is stopped in the G_1 phase.¹³⁷

Combination Chemotherapy

Combination chemotherapy may provide greater efficacy than single-agent therapy by three mechanisms: (a) it provides maximum cell kill within the range of toxicity for each drug that can be tolerated by the host, (b) it offers a broader range of coverage of resistant cell lines in a heterogeneous population, and (c) it prevents or delays the emergence of drug-resistant cell lines.¹³⁷ When combination regimens are devised, drugs known to be active as single agents usually are selected. Drugs with different mechanisms of action are combined to allow for additive or synergistic effects. Combining cell-cycle-specific and cell-cycle-nonspecific agents may be especially advantageous. Drugs with differing dose-limiting toxic effects are combined to allow for

Table 10-10

Classification of chemotherapeutic agents

Alkylating agents*Classic alkylating agents*

Busulfan
 Chlorambucil
 Cyclophosphamide
 Ifosfamide
 Mechlorethamine (nitrogen mustard)
 Melphalan
 Mitomycin C
 Triethylene thiophosphoramide (thiotepa)

Nitrosoureas

Carmustine (BCNU)
 Lomustine (CCNU)
 Semustine (MeCCNU)
 Streptozocin

Miscellaneous DNA-binding agents

Carboplatin
 Cisplatin
 Dacarbazine (DTIC)
 Hexamethylmelamine
 Procarbazine

Antitumor antibiotics

Bleomycin
 Dactinomycin (actinomycin D)
 Daunorubicin
 Doxorubicin
 Idarubicin
 Plicamycin (mithramycin)

Antimetabolites

Folate analogues
 Methotrexate

Purine analogues

Azathioprine
 Mercaptopurine
 Thioguanine
 Cladribine (2-chlorodeoxyadenosine)
 Fludarabine
 Pentostatin

Pyrimidine analogues

Capecitabine
 Cytarabine
 Floxuridine
 Gemcitabine

Ribonucleotide reductase inhibitors

Hydroxyurea

Plant alkaloids*Vinca alkaloids*

Vinblastine
 Vincristine
 Vindesine
 Vinorelbine

Epipodophyllotoxins

Etoposide
 Teniposide

Taxanes

Paclitaxel
 Docetaxel

Miscellaneous agents

Asparaginase
 Estramustine
 Mitotane

each drug to be given at therapeutic doses. Drugs with different patterns of resistance are combined whenever possible to minimize cross-resistance. The treatment-free interval between cycles is kept to the shortest possible time that will allow for recovery of the most sensitive normal tissue.

Drug Toxicity

Tumors are more susceptible than normal tissue to chemotherapeutic agents, in part because they have a higher proportion of dividing cells. Normal tissues with a high growth fraction, such as the bone marrow, oral and intestinal mucosa, and hair follicles, are also sensitive to chemotherapeutic effects. Therefore, treatment with chemotherapeutic agents can produce toxic effects such as bone marrow suppression, stomatitis, ulceration of the GI tract, and alopecia. Toxic effects usually are graded from 0 to 4 on the basis of World Health Organization standard criteria.¹³⁸ Significant drug toxicity may necessitate a dosage reduction. A toxic effect requiring a dose modification or change in dose intensity is referred to as a dose-limiting toxic effect. Because maintaining dose intensity is important to preserve as high a tumor cell kill as possible, several supportive strategies have been developed, such as administration of colony-stimulating factors and erythropoietin to treat poor bone marrow reserve and administration of cytoprotectants such as mesna and amifostine to prevent renal dysfunction.

Administration of Chemotherapy

Chemotherapy usually is administered systemically (IV, IM, SC, or PO). Systemic administration treats micrometastases at widespread sites and prevents systemic recurrence. However, it increases the drug's toxicity to a wide range of organs throughout the body. One method to minimize systemic toxicity while enhancing target organ delivery of chemotherapy is regional administration of chemotherapy. Many of these approaches require surgical access, such as intrahepatic delivery of chemotherapy for hepatic carcinomas or metastatic colorectal cancer using a hepatic artery infusion pump, limb perfusion for extremity melanoma and sarcoma, and intraperitoneal hyperthermic perfusion for pseudomyxoma peritonei. Alternately, percutaneous access may be utilized, such as limb infusion with percutaneously placed catheters.

HORMONAL THERAPY

Some tumors, most notably breast and prostate cancers, originate from tissues whose growth is under hormonal control. The first attempts at hormonal therapy were through surgical ablation of the organ producing the hormones involved, such as oophorectomy for breast cancer. Currently, hormonal anti-cancer agents include androgens, antiandrogens, antiestrogens, estrogens, glucocorticoids, gonadotropin inhibitors, progestins,

aromatase inhibitors, and somatostatin analogues. Hormones or hormone-like agents can be administered to inhibit tumor growth by blocking or antagonizing the naturally occurring substance, such as with the estrogen antagonist tamoxifen. Other substances that block the synthesis of the natural hormone can be administered as alternatives. Aromatase inhibitors, for example, block the peripheral conversion of endogenous androgens to estrogens in postmenopausal women. Hormonal therapy provides a highly tumor-specific form of therapy in sensitive tissues. In breast cancer, estrogen and progesterone receptor status is used to predict the success of hormonal therapy. Androgen receptor is also being pursued as a therapeutic target for breast cancer treatment.

TARGETED THERAPY

Over the past decade, increased understanding of cancer biology has fostered the emerging field of molecular therapeutics. The basic principle of molecular therapeutics is to exploit the molecular differences between normal cells and cancer cells to develop targeted therapies. Thus targeted therapies usually are directed at the processes involved in tumor growth rather than directly targeting the tumor cells. The ideal molecular target would be exclusively expressed in the cancer cells, be the driving force of the proliferation of the cancer cells, and be critical to their survival. A large number of molecular targets are currently being explored, both preclinically and in clinical trials. The major groups of targeted therapy agents are inhibitors of growth factor receptors, inhibitors of intracellular signal transduction, cell-cycle inhibitors, apoptosis-based therapies, and antiangiogenic compounds.

Protein kinases have come to the forefront as attractive therapeutic targets with the success of imatinib mesylate (Gleevec) in treating chronic myelogenous leukemia and GI stromal tumors, and trastuzumab (Herceptin) in treating breast cancer, and vemurafenib in treating melanoma. These drugs work by targeting bcr-abl and c-kit (imatinib) and HER2 and Braf, respectively. For example, recently a phase III randomized trial demonstrated that, compared with dacarbazine, standard of care chemotherapy option for patients with metastatic melanoma with a V600E BRAF mutation, the BRAF inhibitor vemurafenib led to significantly higher response rates (48% vs. 5%).¹³⁹ At 6 months, overall survival was 84% (95% CI, 78 to 89) in the vemurafenib group and 64% (95% CI, 56 to 73) in the dacarbazine group. The hazard ratio for tumor progression in the vemurafenib group was 0.26 (95% CI, 0.20 to 0.33; $P < 0.001$). The estimated median progression-free survival was 5.3 months in the vemurafenib group and 1.6 months in the dacarbazine group. This trial highlights the fact that in at least some tumor types targeted therapies that inhibit a genomic alteration that is a driver is likely to be more effective than an unselected therapeutic option.

Sequencing of the human genome has revealed approximately 500 protein kinases. Several tyrosine kinases have been shown to have oncogenic properties and many other protein kinases have been shown to be aberrantly activated in cancer cells.⁹⁰ Therefore, protein kinases involved in these aberrantly activated pathways are being aggressively pursued in molecular therapeutics. Potential targets like HER2 can be targeted via different strategies, such as transcriptional downregulation, targeting of mRNA, RNA inhibition, antisense strategies, direct inhibition of protein activity, and induction of immunity against the protein.

Most of the compounds in development are monoclonal antibodies like trastuzumab or small-molecule kinase inhibitors like imatinib or vemurafenib. Some other agents, such as sunitinib, are multi-targeted kinase inhibitors. Selected FDA-approved targeted therapies are listed in Table 10-11. Many of the promising pathways, such as the PI3K/Akt/mTOR pathway are being pursued as therapeutic targets with several drugs in development, targeting different aspects of the pathway (Fig. 10-15).¹⁴⁰

Development of molecularly targeted agents for clinical use presents several unique challenges. Once an appropriate compound is identified and confirmed to have activity in pre-clinical testing, predictive markers for activity in the preclinical setting must be defined. Expression of a target may not be sufficient to predict response, because the pathway of interest may not be activated or critical to the cancer's survival. Although in traditional phase I trials the goal is to identify the maximum tolerated dosage, the maximum dosage of biologic agents may not be necessary to achieve the desired biologic effect. Thus assays to verify modulation of the target need to be developed to determine at what dosage the desired effect is achieved. When phase II and III clinical trials are initiated, biomarker modulation studies should be integrated into the trial to determine whether clinical response correlates with target modulation and thus to identify additional parameters that impact response. Rational dose selection and limitation of study populations to patients most likely to respond to the molecular therapy as determined by predictive markers are most likely to lead to successful clinical translation of a product. Finally, most biologic agents are cytostatic, not cytotoxic. Thus rational combination therapy mixing new biologic agents with either established chemotherapeutic agents that have synergy or with other biologic agents is more likely to lead to cancer cures.

IMMUNOTHERAPY

The aim of immunotherapy is to induce or potentiate inherent antitumor immunity that can destroy cancer cells. Central to the process of antitumor immunity is the ability of the immune system to recognize tumor-associated antigens present on human cancers and to direct cytotoxic responses through humoral or T-cell-mediated immunity. Overall, T-cell-mediated immunity appears to have the greater potential of the two for eradicating tumor cells. T cells recognize antigens on the surfaces of target cells as small peptides presented by class I and class II MHC molecules.

Several antitumor strategies are under investigation. One approach to antitumor immunity is nonspecific immunotherapy, which stimulates the immune system as a whole through administration of bacterial agents or their products, such as bacille Calmette-Guérin. This approach is thought to activate the effectors of antitumor response such as natural killer cells and macrophages, as well as polyclonal lymphocytes.¹⁴¹ Another approach to nonspecific immunotherapy is systemic administration of cytokines such as interleukin-2, interferon- α , and interferon- γ . Interleukin-2 stimulates proliferation of cytotoxic T lymphocytes and maturation of effectors such as natural killer cells into lymphokine-activated killer cells. Interferons, on the other hand, exert antitumor effects directly by inhibiting tumor cell proliferation and indirectly by activating host immune cells, including macrophages, dendritic cells, and natural killer cells, and by enhancing human leukocyte antigen (HLA) class I expression on tumor cells.¹⁴¹

Table 10-11

Selected FDA-approved targeted therapies

GENERIC NAME	TRADE NAME	TARGET	FDA-APPROVED INDICATIONS
Ado-trastuzumab emtansine	Kadcyla	HER2	Breast cancer
Axitinib	Inlyta	KIT, FDGFR β , VEGFR1/2/3	RCC
Bevacizumab	Avastin	VEGF	Colorectal cancer, lung cancer, glioblastoma, NSCLC RCC
Bosutinib	Bosulif	ABL	CML(Philadelphia chromosome+)
Cabozantinib	Cometriq	FLT3, KIT, MET, RET, VEGFR2	Medullary thyroid cancer
Cetuximab	Erbix	EGFR	Colorectal cancer (<i>KRAS</i> wild-type) Squamous cell cancer of the head and neck
Dasatinib	Sprycel	ABL, src family, KIT, EPHA2, PDGFR- β	CML
Erlotinib	Tarceva	EGFR	NSCLC, Pancreatic cancer
Everolimus	Afinitor	mTOR	PNET, RCC, Breast cancer. Nonresectable subependymal giant cell astrocytoma associated with tuberous sclerosis
Gefitinib	Iressa	EGFR	NSCLC with known/previous benefit from gefitinib (limited approval)
Imatinib	Gleevec	KIT, ABL, PDGFR	CML, GIST (KIT+), Dermatofibrosarcoma protuberans
Lapatinib	Tykerb	EGFR and HER2	Breast cancer (<i>HER2</i> +))
Nilotinib	Tasigna	ABL	CML (Philadelphia chromosome+)
Panitumumab	Vectibix	EGFR	Colorectal cancer (<i>KRAS</i> wild type)
Pazopanib	Votrient	VEGFR, PDGFR, KIT	RCC
Pertuzumab	Perjeta	HER2	Breast cancer (<i>HER</i> +))
Ponatinib	Iclusig	ABL, FGFR1-3, FLT3, VEGFR2	CML, ALL (Philadelphia chromosome+)
Regorafenib	Stivarga	KIT, PDGFR β , RAF, RET, VEGFR1/2/3	Colorectal cancer, GIST
Sorafenib	Nexavar	VEGFR, PDGFR, KIT, RAF	HCC RCC
Sunitinib	Sutent	VEGFR PDGFR KIT, Flt-3, RET	GIST, RCC, PNET
Temsirolimus	Torisel	mTOR	RCC
Trastuzumab	Herceptin	HER2	Breast cancer (<i>HER2</i> +)) Gastric cancer (<i>HER2</i> +))
Vandetanib	Caprelsa	EGFR, RET, VEGFR2	Medullary thyroid cancer
Vemurafenib	Zelboraf	BRAF	Melanoma (<i>BRAF V600E</i> mutant)

CML, chronic myelogenous leukemia; **EGFR**, epidermal growth factor receptor; **EPHA2**, ephrin A2; **FDA**, Food and Drug Administration; **Flt-3**, fms-related tyrosine kinase 3; **GIST**, GI stromal tumor; **HCC**, Hepatocellular cancer, **HER2**, human epidermal growth factor receptor 2; **mTOR**, mammalian target of rapamycin; **NSCLC**, non-small cell lung cancer; **PDGF**, platelet-derived growth factor; **PDGFR**, platelet-derived growth factor receptor; **PNET**, Pancreatic neuroendocrine tumor, **RCC**, renal cell carcinoma; **RET**, rearranged during transfection; **VEGF**, vascular endothelial growth factor; **VEGFR**, vascular endothelial growth factor receptor.

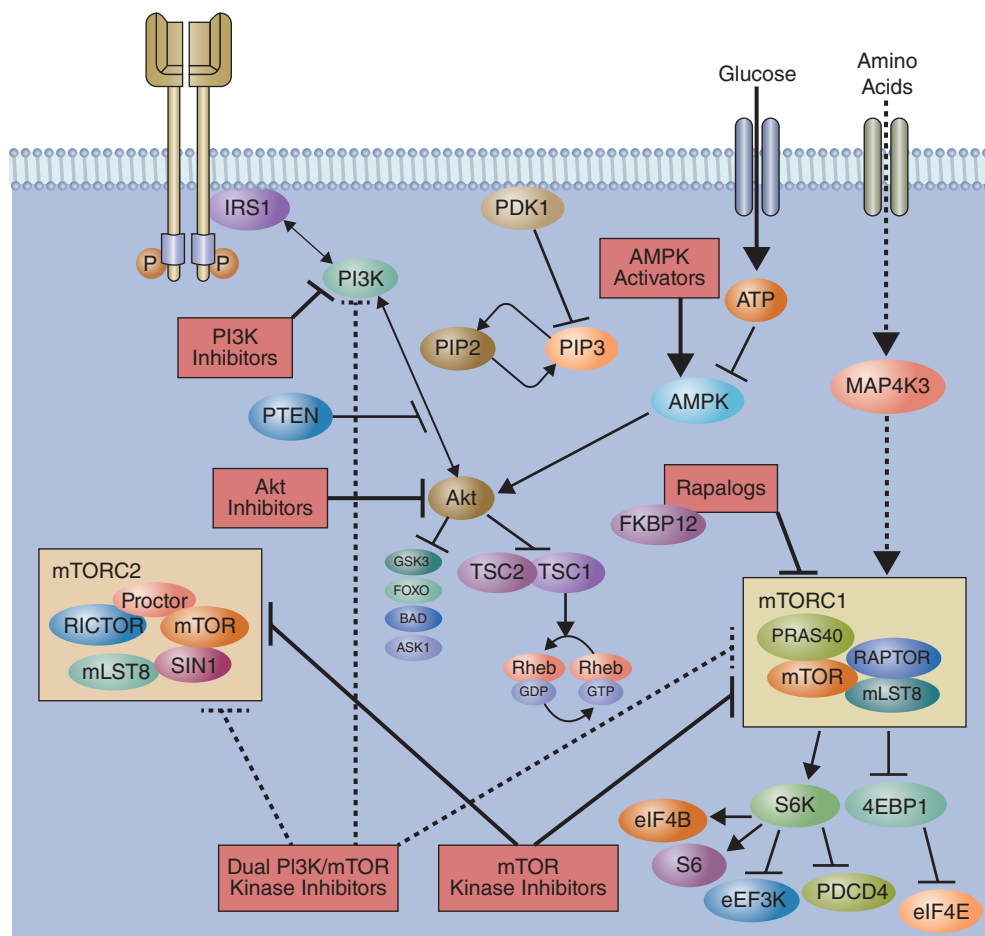


Figure 10-15. Targeting PI3K/Akt/mTOR signaling. This central pathway is altered in many tumor types and is being pursued as a therapeutic target through development of numerous pathway inhibitors targeting PI3K, Akt, mTOR, dual inhibitors as well as several upstream and downstream regulators. (Modified with permission from McAuliffe et al. Copyright Elsevier.)¹⁴⁰

Antigen-specific immunotherapy can be active, as is achieved through antitumor vaccines, or passive. In passive immunotherapy, antibodies to specific tumor-associated antigens can be produced by hybridoma technique and then administered to patients whose cancers express these antigens, inducing antibody-dependent cellular cytotoxicity.

The early attempts at vaccination against cancers used allogeneic cultured cancer cells, including irradiated cells, cell lysates, and shed antigens isolated from tissue culture supernatants. An alternate strategy is the use of autologous tumor vaccines. These have the potential advantage of being more likely to contain antigens relevant for the individual patient but have the disadvantage of requiring a large amount of tumor tissue for preparation, which restricts eligibility of patients for this modality. Strategies to enhance immunogenicity of tumor cells include the introduction of genes encoding cytokines or chemokines, and fusion of the tumor cells to allogeneic MHC class II-bearing cells.¹⁴² Alternatively, heat shock proteins derived from a patient's tumor can be used, because heat shock protein peptide complexes are readily taken up by dendritic cells for presentation to T cells.¹⁴²

Identification of tumor antigens has made it possible to perform antigen-specific vaccination. For example in the case of melanoma, several antigens have been identified that can be recognized by both CD8⁺ cytotoxic T cells and CD4⁺ helper T cells, including MART-1, gp 100, MAGE1, tyrosinase, TRP-1, TRP-2, and NY-ESO-1.¹⁴³ Antigens tested usually are

overexpressed or mutated in cancer cells. Tissue specificity and immunogenicity are important determinants in choosing an appropriate target. Vaccines directed at defined tumor antigens aim to combine selected tumor antigens and appropriate routes for delivering these antigens to the immune system to optimize antitumor immunity.¹⁴⁴ Several different vaccination approaches are under study, including tumor cell-based vaccines, peptide-based vaccines, recombinant virus-based vaccines, DNA-based vaccines, and dendritic cell vaccines.

In adoptive transfer, antigen-specific effector cells (i.e., cytotoxic T lymphocytes) or antigen-nonspecific effector cells (i.e., natural killer cells) can be transferred to a patient. These effector cells can be obtained from the tumor (tumor-infiltrating lymphocytes) or the peripheral blood.

Clinical experience in patients with metastatic disease has shown objective tumor responses to a variety of immunotherapeutic modalities. It is thought, however, that the immune system is overwhelmed with the tumor burden in this setting, and thus adjuvant therapy may be preferable, with immunotherapy reserved for decreasing tumor recurrences. Trials to date suggest that immunotherapy is a potentially useful approach in the adjuvant setting. How to best select patients for this approach and how to integrate immunotherapy with other therapies are not well understood for most cancer types.

Tolerance to self-antigens expressed in tumors is a limitation in generating antitumor responses.¹⁴⁵ Recently, several

pathways that modulate tolerance and approaches to manipulating these pathways have been identified: pathways that activate professional antigen-presenting cells such as Toll-like receptors, growth factors, and the CD40 pathway; cytokines to enhance immunoactivation; and pathways that inhibit T-cell inhibitory signals or Tregs.¹⁴⁵

A new strategy being actively explored involves the use of cytotoxic T-lymphocyte antigen 4 (CTLA-4). CTLA-4 exists on the surfaces of T cells and has a homeostatic immunosuppressive function, downregulating the response of T cells to stimuli.¹⁴⁶

In a recent phase 3 study, ipilimumab—which blocks CTLA-4, was administered with or without glycoprotein 100 (gp100) peptide vaccine and was compared with gp100 alone in HLA-A*0201-positive patients with previously treated metastatic melanoma. The median overall survival was significantly longer for patients receiving ipilimumab with or without gp100, compared with patients who receiving gp100.¹⁴⁷ In another Phase III trial, ipilimumab in combination with dacarbazine, compared with dacarbazine plus placebo, improved overall survival in patients with previously untreated metastatic melanoma.¹⁴⁸ Anti-CTLA-4 antibodies are under study for use in melanoma as well as several other cancer types as single agents, in combination with targeted therapies, interleukin-2, chemotherapy, or peptide vaccines.¹⁴⁶

Programmed death ligand 1 (PD-L1) is a 40kDa type 1 transmembrane protein that is thought to play an important role in suppressing the immune system. PD-L1 binds to its receptor, PD-1, which is found on activated T cells, B cells, and myeloid cells. The PD1/PDL1 pathway is increasingly recognized as a key contributor to tumor-mediated immune suppression. Thus both anti-PD1 and anti-PD-L1 strategies are actively being pursued for cancer therapy.

GENE THERAPY

Gene therapy is being pursued as a possible approach to modifying the genetic program of cancer cells as well as treating metabolic diseases. The field of cancer gene therapy uses a variety of strategies, ranging from replacement of mutated or deleted tumor-suppressor genes to enhancement of immune responses to cancer cells.¹⁴⁹ Indeed, in preclinical models, approaches such as replacement of tumor-suppressor genes leads to growth arrest or apoptosis. However, the translation of these findings into clinically useful tools presents special challenges.

One of the main difficulties in getting gene therapy technology from the laboratory to the clinic is the lack of a perfect delivery system. An ideal vector would be administered through a noninvasive route and would transduce all of the cancer cells and none of the normal cells. Furthermore, the ideal vector would have a high degree of activity, that is, it would produce an adequate amount of the desired gene product to achieve target cell kill. Unlike genetic diseases in which delivery of the gene of interest into only a portion of the cells may be sufficient to achieve clinical effect, cancer requires either that the therapeutic gene be delivered to all of the cancer cells or that a therapeutic effect be achieved on nontransfected cells as well as transfected cells through a bystander effect. But then, treatment of a metabolic disease requires prolonged gene expression, whereas transient expression may be sufficient for cancer therapy.

Several vector systems are under study for gene therapy; however, none is considered ideal. One of the promising approaches to increase the number of tumor cells transduced is the use of a replication-competent virus like a parvovirus,

human reovirus, or vesicular stomatitis virus that selectively replicates within malignant cells and lyses them more efficiently than it does normal cells. Another strategy for killing tumor cells with suicide genes exploits tumor-specific expression elements, such as the MUC-1, PSA, CEA, or VEGF promoters, that can be used to achieve tissue-specific or tumor-specific expression of the desired gene.

Because the goal in cancer therapy is to eradicate systemic disease, optimization of delivery systems is the key to success for gene therapy strategies. Gene therapy is likely to be most successful when combined with standard therapies, but it will provide the advantage of customization of therapy based on the molecular status of an individual's tumor.

MECHANISMS OF INTRINSIC AND ACQUIRED DRUG RESISTANCE

Several tumor factors influence tumor cell kill. Tumors are heterogeneous, and, according to the Goldie-Coldman hypothesis, tumor cells are genetically unstable and tend to mutate to form different cell clones. This has been used as an argument for giving chemotherapy as soon as possible in treatment to reduce the likelihood that resistant clones will emerge. Tumor size is another important variable. Large tumor, may have greater heterogeneity, although heterogeneity may also differ based on biological subtype. Moreover, according to the gompertzian model, cancer cells initially grow rapidly (exponential growth phase), then the growth slows down owing to hypoxia and decreased nutrient supply. Because of the larger proportion of cells dividing, smaller tumors may be more chemosensitive.

Multiple mechanisms of systemic therapy resistance have been identified (Table 10-12).¹⁵⁰ Cells may exhibit reduced sensitivity to drugs by virtue of their cell-cycle distribution. For example, cells in the G₀ phase are resistant to drugs active in the S phase. This phenomenon of “kinetic resistance” usually is temporary, and if the drug level can be maintained, all cells will eventually pass through the vulnerable phase of the cell cycle.¹³⁷ Alternatively, tumor cells may exhibit “pharmacologic resistance,” in which the failure to kill cells is due to insufficient drug concentration. This may occur when tumor cells are located in sites where effective drug concentrations are difficult to achieve (such as the central nervous system) or can be due to enhanced metabolism of the drug after its administration, decreased conversion of the drug to its active form, or decrease in the intracellular drug level caused by increased removal of the drug from the cell associated with enhanced expression of P-glycoprotein, the protein product of multidrug resistance gene 1. Other mechanisms of resistance include decreased affinity of the target enzyme for the drug, altered amount of the target enzyme, or enhanced repair of the drug-induced defect. For drug-sensitive cancers, another factor limiting optimal killing is improper dosing. A dose reduction of 20% because of drug toxicity can lead to a decline in the cure rate by as much as 50%.¹³⁷ Furthermore, a twofold increase in dose can be associated with a tenfold (1 log) increase in tumor cell kill.

Cancer cells demonstrate adaptive responses to targeted therapy, like activating alternate pathways of survival; thus these alterations may blunt therapeutic efficacy. Cancer cells also acquire resistance upon prolonged treatment with targeted therapy through a variety of mechanisms. One mechanism is through the loss of the target. For example, this was observed in a study of patients with *HER2*-positive breast cancer patients

Table 10-12

General mechanisms of drug resistance**Cellular and biochemical mechanisms**

- Decreased drug accumulation
 - Decreased drug influx
 - Increased drug efflux
 - Altered intracellular trafficking of drug
- Decreased drug activation
- Increased inactivation of drug or toxic intermediate
- Increased repair of drug-induced damage to:
 - DNA
 - Protein
 - Membranes
- Alteration of drug targets (quantitatively or qualitatively)
- Alteration of cofactor or metabolite levels
- Alteration of gene expression
 - DNA mutation, amplification, or deletion
 - Altered transcription, posttranscription processing, or translation
 - Altered stability of macromolecules

Mechanisms relevant in vivo

- Pharmacologic and anatomic drug barriers (tumor sanctuaries)
- Host-drug interactions
 - Increased drug inactivation by normal tissues
 - Decreased drug activation by normal tissues
 - Relative increase in normal tissue drug sensitivity (toxicity)

Host-tumor interactions

Source: Modified with permission from Morrow et al.¹⁵⁰

who were treated with neoadjuvant trastuzumab-based chemotherapy.¹⁵¹ Post-neoadjuvant treatment, a third of the samples from patients who did not have a complete pathologic response displayed loss of the *HER2* amplification that had been present in their pretreatment-biopsy specimens¹⁵¹. Another means by which cancers develop resistance is the acquisition of additional genomic aberrations. In lung cancer, a second mutation in EGFR (T790M) and MET amplification have been described as two main mechanisms of drug resistance to EGFR inhibitors erlotinib and gefitinib.¹⁵²⁻¹⁵⁴ Other mechanisms like novel genetic changes, including *HER2* and EGFR amplification, *PIK3CA* mutations, and markers of epithelial-to-mesenchymal transition have also been reported in EGFR inhibitor resistant lung.^{155, 156} Analysis of metastases from patients with colorectal cancer who developed resistance to cetuximab or panitumumab showed the emergence of KRAS amplification in one sample and acquisition of secondary KRAS mutations in 60% of the cases.¹⁵⁷ These studies emphasize the utility of repeat tumor biopsy specimens at the time of relapse or progression to identify mechanisms of resistance and best combinatorial therapies.

RADIATION THERAPY**Physical Basis of Radiation Therapy**

Ionizing radiation is energy strong enough to remove an orbital electron from an atom. This radiation can be electromagnetic, like a high-energy photon, or particulate, such as an electron, proton, neutron, or alpha particle. Radiation therapy is delivered primarily as

high-energy photons (gamma rays and X-rays) and charged particles (electrons). Gamma rays are photons that are released from the nucleus of a radioactive atom. X-rays are photons that are created electronically, such as with a clinical linear accelerator. Currently, high-energy radiation is delivered to tumors primarily with linear accelerators. X-rays traverse the tissue, depositing the maximum dose beneath the surface, and thus spare the skin. Electrons are used to treat superficial skin lesions, superficial tumors, or surgical beds to a depth of 5 cm. Gamma rays typically are produced by radioactive sources used in brachytherapy.

The dose of radiation absorbed correlates with the energy of the beam. The basic unit is the amount of energy absorbed per unit of mass (joules per kilogram) and is known as a *gray* (Gy). One gray is equivalent to 100 rads, the unit of radiation measurement used in the past.

Biologic Basis of Radiation Therapy

Radiation deposition results in DNA damage manifested by single- and double-strand breaks in the sugar phosphate backbone of the DNA molecule.¹⁵⁸ Cross-linking between the DNA strands and chromosomal proteins also occurs. The mechanism of DNA damage differs by the type of radiation delivered. Electromagnetic radiation is indirectly ionizing through short-lived hydroxyl radicals produced primarily by the ionization of cellular hydrogen peroxide (H₂O₂).¹⁵⁸ Protons and other heavy particles are directly ionizing and directly damage DNA.

Radiation damage is manifested primarily by the loss of cellular reproductive integrity. Most cell types do not show signs of radiation damage until they attempt to divide, so slowly proliferating tumors may persist for months and appear viable. Some cell types, however, undergo apoptosis.

The extent of DNA damage after radiation exposure is dependent on several factors. The most important of these is cellular oxygen. Hypoxic cells are significantly less radiosensitive than aerated cells. Because the presence of oxygen is thought to prolong the half-life of free radicals produced by the interaction of X-rays and cellular H₂O₂, indirectly ionizing radiation is less efficacious in tumors with areas of hypoxia.¹⁵⁸ In contrast, radiation damage from directly ionizing radiation is independent of cellular oxygen levels.

The extent of DNA damage from indirectly ionizing radiation is dependent on the phase of the cell cycle. The most radiation-sensitive phases are G₂ and M, whereas G₁ and late S phases are less sensitive. Thus irradiation of a population of tumor cells results in killing of a greater proportion of cells in G₂ and M phases. However, delivery of radiation in divided doses, a concept referred to as *fractionation*, allows the surviving G₁ and S phase cells to progress to more sensitive phases, a process referred to as *reassortment*. In contrast to DNA damage after indirectly ionizing radiation, that after exposure to directly ionizing radiation is less dependent on the cell-cycle phase.¹⁵⁹

Several chemicals can modify the effects of ionizing radiation. These include hypoxic cell sensitizers such as metronidazole and misonidazole, which mimic oxygen and increase cell kill of hypoxic cells.¹⁵⁸ A second category of radiation sensitizers are the thymidine analogues iododeoxyuridine and bromodeoxyuridine. These molecules are incorporated into the DNA in place of thymidine and render the cells more susceptible to radiation damage; however, they are associated with considerable acute toxicity. Several other chemotherapeutic agents sensitize cells to radiation through various mechanisms, including

Radiation Therapy Planning

Radiation therapy is delivered in a homogeneous dose to a well-defined region that includes tumor and/or surrounding tissue at risk for subclinical disease. The first step in planning is to define the target to be irradiated as well as the dose-limiting organs in the vicinity.¹⁶⁰ Treatment planning includes evaluation of alternative treatment techniques, which is done through a process referred to as *simulation*. Once the beam distribution that will best achieve homogeneous delivery to the target volume and minimize the dose to the normal tissue is determined, immobilization devices and markings or tattoos on the patient's skin are used to ensure that each daily treatment is given in the same way. Conventional fractionation is 1.8 to 2 Gy/d, administered 5 days each week for 3 to 7 weeks.

Radiation therapy may be used as the primary modality for palliation in certain patients with metastatic disease, primarily patients with bony metastases. In these cases, radiation is recommended for symptomatic metastases only. However, lytic metastases in weight-bearing bones such as the femur, tibia, or humerus also are considered for irradiation. Another circumstance in which radiation therapy might be appropriate is spinal cord compression due to metastases to the vertebral body that extend posteriorly to the spinal canal.

The goal of adjuvant radiation therapy is to decrease local-regional recurrence rates. Adjuvant radiation therapy can be given before surgery, after surgery, or, in selected cases, during surgery. Preoperative radiation therapy has several advantages. It may minimize seeding of the tumor during surgery and it allows for smaller treatment fields because the operative bed has not been contaminated with tumor cells. Also, radiation therapy for inoperable tumors may achieve adequate reduction to make them operable. The disadvantages of preoperative therapy are an increased risk of postoperative wound healing problems and the difficulty in planning subsequent radiation therapy in patients who have positive surgical margins. If radiation therapy is given postoperatively, it is usually given 3 to 4 weeks after surgery to allow for wound healing. The advantage of postoperative radiation therapy is that the surgical specimen can be evaluated histologically and radiation therapy can be reserved for patients who are most likely to benefit from it. Further, the radiation therapy can be modified on the basis of margin status. The disadvantages of postoperative radiation therapy are that the volume of normal tissue requiring irradiation may be larger owing to surgical contamination of the tissue planes and that the tumor may be less sensitive to radiation owing to poor oxygenation. Postlaparotomy adhesions may decrease the mobility of the small bowel loops, increasing the risk for radiation injury in abdominal or pelvic irradiation. Given the potential advantages and disadvantages of both approaches, the roles of preoperative and postoperative radiation therapy are being actively evaluated and compared for many cancer types.

Another mode of postoperative radiation therapy is brachytherapy. In brachytherapy, unlike in external beam therapy, the radiation source is in contact with the tissue being irradiated. The radiation source may be cesium, gold, iridium, or radium. Brachytherapy is administered via temporary or permanent delivery implants such as needles, seeds, or catheters. Temporary brachytherapy catheters are placed either during open surgery or percutaneously soon after surgery. The implants

are loaded interstitially, and treatment usually is given postoperatively for a short duration, such as 1 to 3 days. Although brachytherapy has the disadvantages of leaving scars at the catheter insertion site and requiring special facilities for inpatient brachytherapy the advantage of patient convenience owing to the shorter treatment duration, has made intracavitary treatment approaches very popular for the treatment of breast cancer.

Another short delivery approach is intraoperative radiotherapy (IORT), often used in combination with external beam therapy. The oncologic consequences of the limited treatment volume and duration associated with brachytherapy and IORT are not well understood. Accelerated partial breast irradiation with interstitial brachytherapy, intracavitary brachytherapy (MammoSite), IORT, and three-dimensional conformal external beam radiotherapy is being compared with whole breast irradiation in an intergroup phase III trial (NSABP B-39/Radiation Therapy Oncology Group 0413). Several additional studies of adjuvant IORT also are ongoing internationally. There has also been increasing interest in utilizing intensity-modulated radiation therapy (IMRT). IMRT is a complex technique for the delivery of radiation therapy preferentially to target structures while minimizing doses to adjacent normal critical structures.¹⁶¹ It is widely utilized for the treatment of a variety of tumor types, including the central nervous system, head and neck, breast, prostate, gastrointestinal tract, and gynecologic organs, as well as in patients where previous radiation therapy has been delivered.

It is thought that chemotherapy given concurrently with radiation improves survival rates. Chemotherapy before radiation has the advantage of reducing the tumor burden, which facilitates radiation therapy. On the other hand, some chemotherapy regimens, when given concurrently with radiation, may sensitize the cells to radiation therapy. Chemoradiation is being pursued in many tumor types, including rectal cancer, pancreatic cancer, and esophageal cancer.¹⁶²⁻¹⁶⁴ In a recent Cochrane review of six randomized controlled trials, it was demonstrated that in patients T3/4 rectal cancer, chemoradiation was associated with a significantly lower local recurrence rate compared with radiation therapy alone (OR 0.56, 95% CI 0.42-0.75, $P < 0.0001$), but was not associated with improved survival.¹⁶²

Side Effects

Both tumor and normal tissue have radiation dose-response relationships that can be plotted as a sigmoidal curve (Fig. 10-16).¹⁶⁰ A minimum dose of radiation must be given before any response is seen. The response to radiation then increases slowly with an increase in dose. At a certain dose level the curves become exponential, with increases in tumor response and normal tissue toxicity with each incremental dose increase. The side effects of radiation therapy can be acute, occurring during or 2 to 3 weeks after therapy, or chronic, occurring weeks to years after therapy. The side effects depend on the tissue included in the target volume. Some of the major acute and chronic sequelae of radiation are summarized in Table 10-13.^{160, 165} In addition to these effects, a small increase in the risk for secondary malignancies is attributable to radiation therapy.

CANCER PREVENTION

The truth of the old axiom, "An ounce of prevention is worth a pound of cure" is being increasingly recognized in oncology. Cancer prevention can be divided into three categories: (a) primary prevention (i.e., prevention of initial cancers in healthy

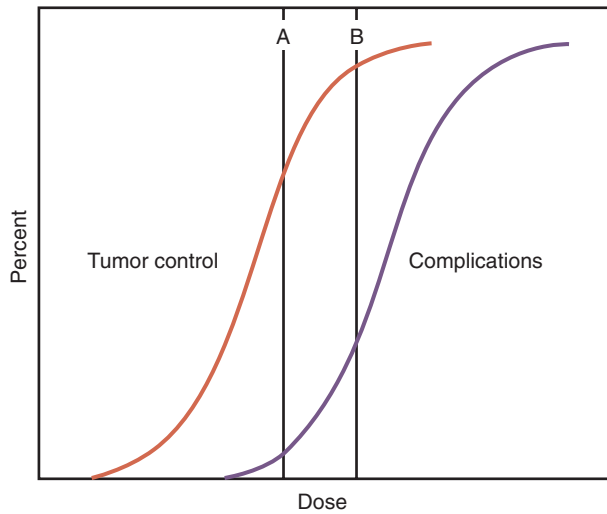


Figure 10-16. The probability of tumor control and of complications at different radiation doses. **A.** At lower doses, the probability of complications is low, with a moderate chance of tumor control. **B.** Increasing the dose may gain a higher chance of tumor control at the price of significantly higher complication risks. (Modified with permission from Eisbruch A, Lichter AS. With kind permission from Springer Science and Business Media.)¹⁶⁰

individuals), (b) secondary prevention (i.e., prevention of cancer in individuals with premalignant conditions), and (c) tertiary prevention (i.e., prevention of second primary cancers in patients cured of their initial disease).

The systemic or local administration of therapeutic agents to prevent the development of cancer, called *chemoprevention*, is being actively explored for several cancer types. In breast cancer, the NSABP Breast Cancer Prevention Trial demonstrated that tamoxifen administration reduces the risk of breast cancer by one half and reduces the risk of estrogen receptor-positive tumors by 69% in high-risk patients.¹⁶⁶ Therefore, tamoxifen has been approved by the FDA for breast cancer chemoprevention.

The subsequent NSABP P-2 trial demonstrated that raloxifene is as effective as tamoxifen in reducing the risk of invasive breast cancer and is associated with a lower risk of thromboembolic events and cataracts but a non-statistically significant higher risk of noninvasive breast cancer; these findings led the FDA to approve raloxifene for prevention as well. Several other agents are also under investigation.¹⁶⁷ Celecoxib has been shown to reduce polyp number and polyp burden in patients with FAP, which led to its approval by the FDA for these patients. In head and neck cancer, 13-*cis*-retinoic acid has been shown both to reverse oral leukoplakia and to reduce second primary tumor development.^{168, 169} Thus, the chemoprevention trials completed so far have demonstrated success in primary, secondary, and tertiary prevention. Although the successes of these chemoprevention studies are impressive, much remains to be done over the next few years to improve patient selection and decrease therapy-related toxic effects. It is important for surgeons to be aware of these preventive options, because they are likely to be involved in the diagnosis of premalignant and malignant conditions and will be the ones to counsel patients about their chemopreventive options.

In selected circumstances, the risk of cancer is high enough to justify surgical prevention. These high-risk settings include hereditary cancer syndromes such as hereditary breast-ovarian cancer syndrome, hereditary diffuse gastric cancer, multiple endocrine neoplasia type 2, FAP, and hereditary nonpolyposis colorectal cancer, as well as some nonhereditary conditions such as chronic ulcerative colitis. Most prophylactic surgeries are large ablative surgeries (e.g., bilateral risk-reducing mastectomy or total proctocolectomy). Therefore, it is important that the patient be completely informed about potential surgical complications as well as long-term lifestyle consequences. Further, the conservative options of close surveillance and chemoprevention need to be discussed. The patient's cancer risk needs to be assessed accurately and implications for survival discussed. Ultimately, the decision to proceed with surgical prevention should be individualized and made with caution.

Table 10-13

Local effects of radiation

ORGAN	ACUTE CHANGES	CHRONIC CHANGES
Skin	Erythema, wet or dry desquamation, epilation	Telangiectasia, subcutaneous fibrosis, ulceration
GI tract	Nausea, diarrhea, edema, ulceration, hepatitis	Stricture, ulceration, perforation, hematochezia
Kidney	—	Nephropathy, renal insufficiency
Bladder	Dysuria	Hematuria, ulceration, perforation
Gonads	Sterility	Atrophy, ovarian failure
Hematopoietic tissue	Lymphopenia, neutropenia, thrombocytopenia	Pancytopenia
Bone	Epiphyseal growth arrest	Necrosis
Lung	Pneumonitis	Pulmonary fibrosis
Heart	—	Pericarditis, vascular damage
Upper aerodigestive tract	Mucositis, xerostomia, anosmia	Xerostomia, dental caries
Eye	Conjunctivitis	Cataract, keratitis, optic nerve atrophy
Nervous system	Cerebral edema	Necrosis, myelitis

Cancer Screening and Diagnosis

It is clear that the practice of oncology will change dramatically over the next few decades, because our understanding of the molecular basis of cancer and available technologies are evolving rapidly. One of the critical changes expected is earlier detection of cancers. With improvements in available imaging modalities and development of newer functional imaging techniques, it is likely that many tumors will be detected at earlier, more curable stages in the near future.

Another area of rapid development is the identification of serum markers. High-throughput technologies such as matrix-assisted laser desorption ionization time-of-flight mass spectroscopy and liquid chromatography ion-spray tandem mass spectroscopy have revolutionized the field of proteomics and are now being used to compare the serum protein profiles of patients with cancer with those of individuals without cancer. Identification of unique proteins as well as unique proteomic profiles for most cancer types is being pursued actively by many researchers and, if successful, could dramatically enhance our ability to detect cancers early.¹⁷⁰ In addition, there is greater interest placed in leveraging circulating free DNA as a potential approach for cancer screening.

Surgical Therapy

The current trend in surgery is toward more conservative resections. With earlier identification of tumors, more conservative operations may be possible. The goal, however, is always to remove the tumor en bloc with wide negative margins. Another interesting area being explored is the destruction of tumors by techniques such as radiofrequency ablation, cryoablation, and heat-producing technologies like lasers, microwaves, or focused ultrasound. Pilot studies have demonstrated that radiofrequency ablation is effective for destruction of small primary breast cancers. Although this approach remains experimental and potentially of limited applicability because of the need for expertise in breast imaging, the development of imaging technologies that can accurately map the extent of cancer cells, these types of noninvasive interventions are likely to come to the forefront. However, use of these techniques will be limited to treatment of cancers not involving hollow viscera.

The debate over how to manage the regional lymph node basins for certain cancer types continues. With an increasing understanding of the metastatic process, surgeons may be able to stratify patients on the basis of the likelihood that their disease will spread metastatically, based on the gene expression profile of their primary tumors, and offer regional therapy accordingly. There is also a growing interest in minimally invasive surgical treatments for a variety of cancer types.

Systemic Therapy

The current trend in systemic therapy is toward individualized therapy. It is now presumed that all cancers of a certain cell origin are the same. Thus all patients are offered the same systemic therapy. Not all patients respond to these therapies; however, this emphasizes the biologic variability within the tumor groups. Therefore, the intent is to determine the underlying biology of each tumor to tailor therapy accordingly. Genomic, transcriptional, and proteomic profiling approaches are being used to identify molecular signatures that correlate with response to certain agents. It is likely that in the near future all tumors can be

tested and treatments individualized. Patients who will respond to conventional therapies can be treated with these regimens, whereas patients who will not respond will not, which spares them the toxicity. Instead, the latter patients can be offered novel therapies. Furthermore, with emerging biologic therapies, it is likely that patients may be given a combination of biologic therapies that specifically target the alterations in their own tumors. Patients can be genotyped for critical alleles that may affect drug metabolism and thus, may influence the efficacy as well as the side effect of the drugs given. Finally, stratification of patients by gene expression profile for prognosis may assist in determining which patients are at higher risk of relapse, so that patients whose tumors have less aggressive biologic characteristics can be spared further therapy.

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11 chapter

Transplantation

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BACKGROUND

Organ transplantation is a relatively novel field of medicine that has made significant progress since the second half of the twentieth century. Advances in surgical technique and a better understanding of immunology are the two main reasons that transplants have evolved from experimental procedures, just several decades ago, to a widely accepted treatment today for patients with end-stage organ failure. Throughout the world, for a variety of indications, kidney, liver, pancreas, intestine, heart, and lung transplants are now the current standard of care.

But the success of transplantation has created new challenges. A better understanding of the pathophysiology of end-stage organ failure as well as advances in critical care medicine and in the treatment of various diseases led to expanding the criteria for, and decreasing the contraindications to, transplants.

As a result, the discrepancy between the ever-growing number of patients awaiting a transplant and the limited number of organs available is one of the biggest challenges (Fig. 11-1). In 2009 alone, according to the United Network for Organ Sharing (UNOS), about 105,000 patients in the United States were awaiting a transplant, yet the number of transplants performed was only about 28,000 (Fig. 11-2).

DEFINITIONS

In addition to being the overall name of this relatively new field of medicine, *transplantation* is the process of transferring an organ, tissue, or cell from one place to another. An *organ transplant* is a surgical procedure in which a failing organ is replaced by a functioning one. The organ is transplanted either orthotopically (implanted in the same anatomic location in the recipient as it was in the donor) or heterotopically (implanted in

Key Points

- 1▶ The field of transplantation has made tremendous advances in the last 50 years, mainly due to refinements in surgical technique and development of effective immunosuppressive medications.
- 2▶ Although immunosuppressive medications are essential for transplantation, they are associated with significant short- and long-term morbidity.
- 3▶ Opportunistic infections can be significantly lowered by the use of appropriate antimicrobial agents.
- 4▶ Kidney transplantation represents the treatment of choice for almost all patients with end-stage renal disease. The gap between demand (patients on the waiting list) and supply (available kidneys) continues to widen.
- 5▶ Pancreas transplantation represents the most reliable way to achieve euglycemia in patients with poorly controlled diabetes.
- 6▶ The results of islet transplantation continue to improve but still trail those of pancreas transplantation.
- 7▶ Liver transplantation has become the standard of care for many patients with end-stage liver failure and/or liver cancer.

another anatomic location). Orthotopic transplants require the removal of the diseased organ (heart, lungs, liver, or intestine); in heterotopic transplants, the diseased organ is kept in place (kidney, pancreas).

According to the degree of immunologic similarity between the donor and recipient, transplants are divided into three main categories: (a) An *autotransplant* is the transfer of cells, tissue, or an organ from one part of the body to another part in the same person, so no immunosuppression is required. This type of transplant includes skin and vein, bone, cartilage, nerve, and islet cell transplants. (b) An *allograft* is the transfer of cells, tissue, or an organ from one person to another of the same species. The immune system of the recipient recognizes the donated organ as a foreign body, so immunosuppression is required in order to avoid rejection. (c) A *xenograft* is the transfer of cells, tissue, or an organ from one organism to another from a different species. To date, animal-to-human transplants are still experimental procedures, given the very complex immunologic and infectious issues that have yet to be solved.

HISTORY

Over the centuries, multiple references to transplantation can be found in the literature. Yet transplantation as a recognized scientific and medical field began to emerge only in the middle of the twentieth century. Two major events preceded the rise of transplantation.

First, the surgical technique of the vascular anastomosis was developed by French surgeon Alexis Carrel.¹ This led to increased transplant activity, especially in animal models. Russian surgeon Yu Yu Voronoy was the first to report a series of human-to-human kidney transplants in the 1940s.² But the outcomes were dismal, mainly because of the lack of understanding of the underlying immunologic processes.

Second, the findings of British scientist Sir Peter B. Medawar in the 1940s were also key.³ In his work with skin grafts in animal models and in human burn patients, he learned that the immune system plays a crucial role in the failure of skin grafts. His research led to a better understanding of the immune system and is considered to be the birth of transplant immunobiology.

The first human transplant with long-term success was performed by Joseph Murray in Boston, Massachusetts, in 1954.⁴ Because it was a living related kidney transplant between identical twins, no immunosuppression was required; the recipient lived for another 8 years before he died of issues unrelated to the transplanted kidney. Other centers performed similar transplants and could reproduce the good results.

Ultimately, attempts were made to perform kidney transplants between nonidentical individuals. For immunosuppression, total-body radiation and an anticancer agent called 6-mercaptopurine were used; given the profound toxicity of both those methods of immunosuppression, results were discouraging. A breakthrough was achieved in the early 1960s with

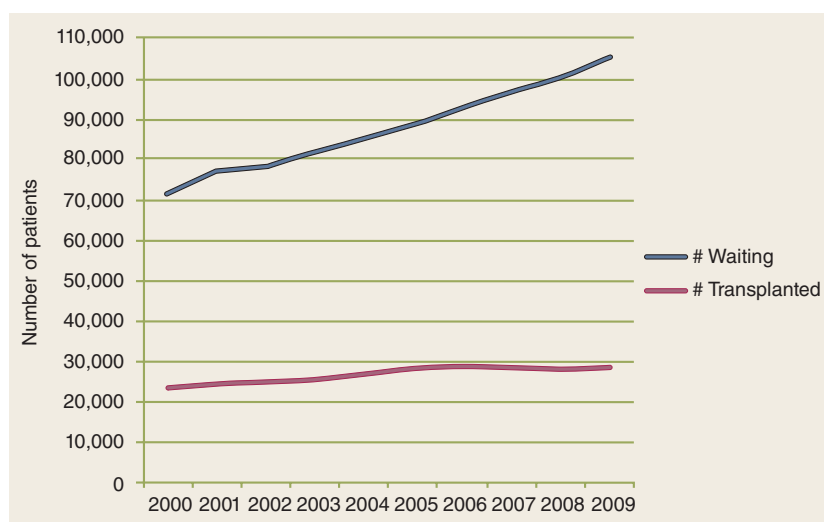


Figure 11-1. Patients on the waiting list and the number of organ transplants performed, 2000 to 2009. (U.S. data from the Scientific Registry of Transplant Recipients Annual Report, <http://srrtr.org>)

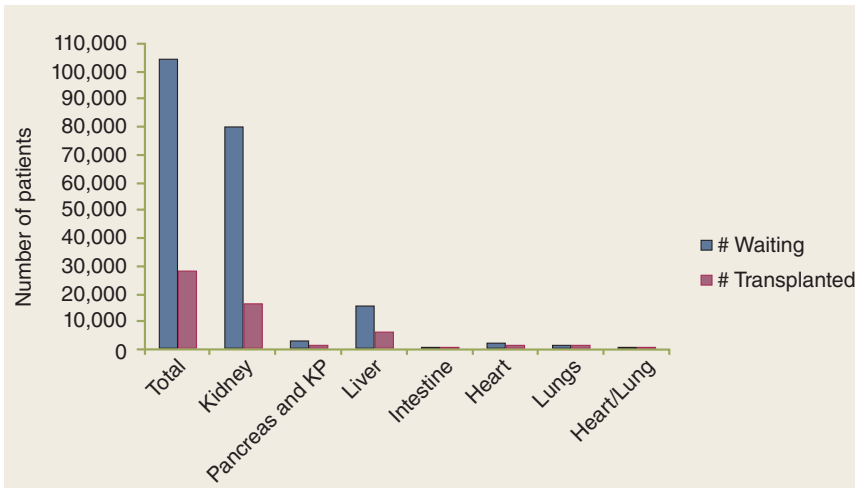


Figure 11-2. Patients on the waiting list and the number of organ transplants performed, 2009. KP = kidney and pancreas. (U.S. data from the Scientific Registry of Transplant Recipients Annual Report, <http://srtr.org>)

the introduction of maintenance immunosuppression through a combination of corticosteroids and a less toxic derivative of 6-mercaptopurine, azathioprine.^{5,6}

Increasing experience with kidney transplants and the better results achieved with maintenance immunosuppression paved the way for the era of extrarenal transplants (Table 11-1). In 1963, the first liver transplant was performed by Thomas Starzl in Denver, Colorado, and the first lung transplant was performed by James Hardy in Jackson, Mississippi. In 1966, the first pancreas transplant was performed by William Kelly and Richard Lillehei in Minneapolis, Minnesota. In 1967, the first successful heart transplant was performed by Christiaan Barnard in Cape Town, South Africa. The early years of transplantation were marked by high mortality, mainly because of irreversible rejection. Dramatic changes occurred with the further development of immunosuppression. The groundbreaking event was the introduction of the first anti-T lymphocyte (T cell) drug, cyclosporine, in the early 1980s.⁷ Since then, with an even better understanding of immunologic processes, many other drugs have been introduced that target specific pathways of rejection. As a result, rejection rates have decreased substantially, allowing a 1-year graft survival rate in excess of 80% in all types of transplants.

The gradual increase in the organ shortage led to innovative surgical techniques. For example, deceased donor split-liver

transplants and living donor liver transplants have helped expand the liver donor pool. Similarly, living donor intestine and pancreas techniques have been developed. The evolution of donor nephrectomy from an open to a minimally invasive procedure (laparoscopic or robotic) has helped increase the pool of living kidney donors.

TRANSPLANT IMMUNOBIOLOGY

The outcomes of early transplants were unsatisfactory. The limiting factor was the lack of understanding of immunologic processes. Irreversible rejection was the reason for graft loss in the vast majority of recipients. A better understanding of transplant immunobiology led to significant improvements in patient and graft survival rates.^{8,9} The immune system is designed as a defense system to protect the body from foreign pathogens, such as viruses, bacteria, and fungi, but it also acts to reject transplanted cells, tissues, and organs, recognizing them as foreign. It mediates other complex processes as well, such as the body's response to trauma or to tumor growth. No matter what the pathogen is, the immune system recognizes it as a foreign antigen and triggers a response that eventually leads either to death or to rejection of the pathogen.

Table 11-1

Transplant history

ORGAN	YEAR	SURGEON	LOCATION
Kidney	1954	Joseph E. Murray	Boston, MA
Liver	1963	Thomas E. Starzl	Denver, CO
Lung	1963	James D. Hardy	Jackson, MS
Pancreas	1966	Richard C. Lillehei	Minneapolis, MN
Heart	1967	Christiaan N. Barnard	Cape Town, South Africa
Small intestine	1967	Richard C. Lillehei	Minneapolis, MN
Heart/lung	1981	Bruce Reitz	Stanford, CA
Multivisceral	1989	Thomas E. Starzl	Pittsburgh, PA

TRANSPLANT ANTIGENS

Transplants between genetically nonidentical persons lead to recognition and rejection of the organ by the recipient's immune system, if no intervention is undertaken. The main antigens responsible for this process are part of the major histocompatibility complex (MHC). In humans, these antigens make up the human leukocyte antigen (HLA) system. The antigen-encoding genes are located on chromosome 6. Two major classes of HLA antigens are recognized. They differ in their structure, function, and tissue distribution. Class I antigens (HLA-A, HLA-B, and HLA-C) are expressed by all nucleated cells. Class II antigens (HLA-DR, HLA-DP, and HLA-DQ) are expressed by antigen-presenting cells (APCs) such as B lymphocytes, dendritic cells, macrophages, and other phagocytic cells.

The principal function of HLA antigens is to present the fragments of foreign proteins to T lymphocytes. This leads to recognition and elimination of the foreign antigen with great specificity. HLA molecules play a crucial role in transplant recipients as well. They can trigger rejection of a graft via two different mechanisms. The most common mechanism is cellular rejection, in which the damage is done by activated T lymphocytes. The process of activation and proliferation is triggered by exposure of T lymphocytes to the donor's HLA molecules. The other mechanism is humoral rejection, in which the damage is done by circulating antibodies against the donor's HLA molecules. The donor-specific antibodies can be present either pretransplant, due to previous exposure (because of a previous transplant, pregnancy, blood transfusion, or immunization), or posttransplant. After binding to the donor's HLA molecules, the complement cascade is activated, leading to cellular lysis.

ALLORECOGNITION AND LYMPHOCYTE ACTIVATION

The immune system of each person is designed to discriminate between self and nonself cells and tissues. This process is called allorecognition, with T cells playing the crucial role. The recognition of foreign HLA antigens by the recipient's T cells may occur by either a direct or an indirect pathway. Direct recognition occurs when the recipient's T cells are activated by direct interaction with the donor's HLA molecules. Indirect recognition occurs when the recipient's T cells are activated by interaction with APCs that have processed and presented the foreign antigen. The foreign antigen can be shed from the graft into the circulation, or it can be identified by the APCs in the graft itself.

Independent of the pathway of foreign HLA antigen presentation, the ensuing activation of T cells is similar. A two-signal model, T-cell activation begins with the engagement of the T-cell receptor (TCR)/CD3 complex with the foreign molecule. This interaction causes transmission of the signal into the cell, named signal 1. However, this signal alone is not sufficient to activate the T cell. An additional costimulatory signal is required, named signal 2. Two well-characterized costimulatory interactions are the CD40/CD154 and B7/CD28 pathways. The "master switch" is turned on by the interaction of CD40 protein with APCs, along with the interaction of CD154 protein with T cells; this ligation induces the upregulation of other costimulatory molecules. Transmission of signal 1 and signal 2 into the cell nucleus leads to upregulation of the transcription of genes for several cytokines, including the T-cell growth factor interleukin-2 (IL-2). In turn, IL-2 activates a number of pathways, leading to proliferation and

differentiation of T cells. Rejection is a result of an attack of activated T cells on the transplanted organ.

Although T-cell activation is the main culprit in rejection, B-cell activation and subsequent antibody production also play a role. After the foreign HLA antigen is processed by B cells, it interacts with activated helper T cells, leading to differentiation of B cells into plasma cells and subsequently to their proliferation and antibody production.

CLINICAL REJECTION

Graft rejection is due to a complex interaction of different parts of the immune system, including B and T lymphocytes, APCs, and cytokines. The end result is graft damage caused by inflammatory injury. According to its onset and pathogenesis, rejection is divided into three main types: *hyperacute*, *acute*, and *chronic* (each described in the following sections).

Hyperacute

Hyperacute rejection, a very rapid type of rejection, results in irreversible damage and graft loss within minutes to hours after organ reperfusion. It is triggered by preformed antibodies against the donor's HLA or ABO blood group antigens. These antibodies activate a series of events that result in diffuse intravascular coagulation, causing ischemic necrosis of the graft. Fortunately, pretransplant blood group typing and cross-matching (in which the donor's cells are mixed with the recipient's serum, and then destruction of the cells is observed) have virtually eliminated the incidence of hyperacute rejection.

Acute

Acute rejection, the most common type of rejection, usually occurs within a few days or weeks posttransplant. According to the mechanism involved, it is further divided into cellular (T-cell-mediated) rejection, humoral (antibody-mediated) rejection, or a combination of both. The diagnosis is based on the results of biopsies of the transplanted organ, special immunologic stains, and laboratory tests (such as elevated creatinine levels in kidney transplant recipients, elevated liver function values in liver transplant recipients, and elevated levels of glucose, amylase, and lipase in pancreas transplant recipients).

Chronic

Chronic rejection is a slow type of rejection. It can manifest within the first year posttransplant, but most often progresses gradually over several years. The mechanism is not well understood, but the pathologic changes eventually lead to fibrosis and loss of graft function. With advances in immunosuppression, this relatively rare form of rejection is becoming more common.

CLINICAL IMMUNOSUPPRESSION

A successful transplant is a balance between the recipient's immune response, the donor's allograft, and pharmacologic immunosuppression. Immunosuppressive regimens are very important to graft and patient survival posttransplant.

2► Immunosuppression has evolved from the use of azathioprine and steroids in the 1960s and 1970s to the development, in the 1980s, of cyclosporine, which increased allograft survival.^{10,11} The introduction of tacrolimus and mycophenolate mofetil (MMF) in the 1990s further changed the field of transplantation, enabling a variety of combinations to be used for immunosuppression (Table 11-2).

Table 11-2

Immunosuppressive drugs by grouping**Immunophilin binders**

- Calcineurin inhibitors
 - Cyclosporine
 - Tacrolimus
- Noninhibitors of calcineurin
 - Sirolimus

Antimetabolites

- Inhibitors of de novo purine synthesis
 - Azathioprine
 - Mycophenolate mofetil

Biologic immunosuppression

- Polyclonal antibodies
 - Atgam
 - Antithymocyte immunoglobulin
- Monoclonal antibodies
 - Muromonab-CD3
 - Basiliximab
 - Belatacept
 - Alemtuzumab
 - Rituximab
 - Bortezomib
 - Ecilizumab

Other

- Corticosteroids

Immunosuppressants usually are used in multidrug regimens, aimed at increasing efficacy by targeting multiple pathways to lower the immune response and to decrease the toxicity of individual agents. Certain regimens may involve withdrawal, avoidance, or minimization of certain classes of drugs. Transplant centers generally institute their immunosuppressive protocols based on experience, risk profiles, cost considerations, and outcomes. Immunosuppression is delivered in two phases: induction (starting immediately posttransplant, when the risk of rejection is highest) and maintenance (usually starting within days posttransplant and continuing for the life of the recipient or graft). Thus, the level of immunosuppression is highest in the first 3 to 6 months posttransplant; during this time, prophylaxis against various bacterial, viral, or even antifungal opportunistic infections is also given.^{12,13}

A conventional immunosuppressive protocol might include (a) induction with anti-T-lymphocyte-depleting or nondepleting antibodies and (b) maintenance with calcineurin inhibitors, antiproliferative agents, and corticosteroids. Characteristics of the most common immunosuppressive agents are listed in Table 11-3.

INDUCTION

Induction includes the use of depleting (polyclonal) antibodies or nondepleting antibodies within the first month posttransplant. Studies have shown that induction with antibody regimens may prevent acute rejection, potentially leading to improved graft survival and the use of less maintenance immunosuppression.

Depleting Antibodies

Rabbit antithymocyte globulin (Thymoglobulin) is a purified gamma globulin obtained by immunizing rabbits with human

thymocytes. Atgam, which has largely been replaced by Thymoglobulin, is a purified gamma globulin obtained by immunizing horses with human thymocytes. These agents contain antibodies to T cells and B lymphocytes (B cells), integrins, and other adhesion molecules, thereby resulting in rapid depletion of peripheral lymphocytes. Typically, the total dose of Thymoglobulin is roughly 6 mg/kg, a dose that has been shown to confer adequate lymphocyte depletion and better allograft survival. Doses of 3 mg/kg may not effectively prevent acute rejection, but more doses and prolonged duration increase the risk of infection and the potential occurrence of lymphoma. Thymoglobulin administration causes a cytokine release syndrome, so premedications (acetaminophen and diphenhydramine) are usually given. The principal side effects of Thymoglobulin include fever, chills, arthralgias, thrombocytopenia, leukopenia, and an increased incidence of a variety of infections.^{14,15}

Nondepleting Antibodies

Basiliximab (Simulect) is an anti-CD25 monoclonal antibody. The alpha subunit of the IL-2 receptor, also known as *Tac* or *CD25*, is found exclusively on activated T cells. Blockade of this component by monoclonal antibody selectively prevents IL-2–induced T-cell activation. No lymphocyte depletion occurs with basiliximab; it is not designed to be used to treat acute rejection. Its selectivity in blocking IL-2–mediated responses makes it a powerful induction agent without the added risks of infections, malignancies, or other major side effects. Currently, basiliximab is the only available anti-CD25 monoclonal antibody approved for clinical use. Usually, it is followed by the use of calcineurin inhibitors, corticosteroids, and MMF as maintenance immunosuppression.¹⁶

Alemtuzumab (Campath), another anti-CD52 monoclonal antibody, was initially used to treat chronic lymphocytic leukemia. The use of alemtuzumab has grown in the field of transplantation, given its profound lymphocyte-depleting effects. It causes cell death by complement-mediated cytotoxicity, antibody-mediated cytotoxicity, and apoptosis. One dose alone (30 mg) depletes 99% of lymphocytes. Monocyte recovery can be seen at 3 months posttransplant; B-cell recovery at 12 months; and T-cell recovery, albeit only to 50% of baseline, at 36 months. Alemtuzumab causes a significant cytokine release reaction and often requires premedications (steroids and antihistamines). Because of the long-lasting T-cell depletion, the risks of infection and posttransplant lymphoproliferative disorder remain. Currently, alemtuzumab is available only through a limited distribution program, not through commercial medication distributors.^{17,18}

MAINTENANCE**Corticosteroids**

Corticosteroids have had a role in immunosuppression since the beginning of the field of transplantation. Despite numerous attempts to limit or discontinue their use, they remain an integral component of most immunosuppressive protocols, for both induction and maintenance. Moreover, they are often the first-line agents in the treatment of acute rejection. Steroids bind to glucocorticoid-responsive elements in DNA that prevent the transcription of cytokine genes and cytokine receptors. In addition, steroids have an impact on lymphocyte depletion, on decreases in cell-mediated immunity, and on T-cell activation of many phases of rejection.

Table 11-3

Summary of the main immunosuppressive drugs

DRUG	MECHANISM OF ACTION	ADVERSE EFFECTS	CLINICAL USES	DOSAGE
Cyclosporine (CSA)	Binds to cyclophilin Inhibits calcineurin and IL-2 synthesis	Nephrotoxicity Tremor Hypertension Hirsutism	Improved bioavailability of microemulsion form	Oral dose 5 mg/kg per day (given in two divided doses)
Tacrolimus (FK506)	Binds to FKBP Inhibits calcineurin and IL-2 synthesis	Nephrotoxicity Hypertension Neurotoxicity GI toxicity (nausea, diarrhea)	Improved patient and graft survival in (liver) primary immunosuppression and rescue therapy Used as mainstay of maintenance protocols	IV 0.015 mg/kg per day as continuous infusion PO 0.05 mg/kg per day (given every 12 h)
Mycophenolate mofetil	Antimetabolite Inhibits enzyme necessary for de novo purine synthesis	Leukopenia GI toxicity	Effective for primary immunosuppression in combination with tacrolimus	1 g bid PO
Sirolimus	Inhibits lymphocyte effects driven by IL-2 receptor	Thrombocytopenia Increased serum cholesterol/LDL Poor wound healing	May allow early withdrawal of steroids and decreased calcineurin doses	2–4 mg/d, adjusted to trough drug levels
Corticosteroids	Multiple actions Anti-inflammatory Inhibits lymphokine production	Cushingoid state Glucose intolerance Osteoporosis	Used in induction, maintenance, and treatment of acute rejection	Varies from milligrams to several grams per day Maintenance doses, 5–10 mg/d
Azathioprine	Antimetabolite Interferes with DNA and RNA synthesis	Thrombocytopenia Neutropenia Liver dysfunction	Used in maintenance protocols or if intolerance to mycophenolate mofetil	1–3 mg/kg per day for maintenance
Belatacept	T-cell blocker	Increased risk of bacterial infections	New drug for maintenance immunosuppression in renal transplants only	5–10 mg/kg per day infusion

FKBP = FK506-binding protein; GI = gastrointestinal; IL = interleukin; IV = intravenous; LDL = low-density lipoprotein; PO = oral

Nonetheless, the numerous adverse effects of steroid therapy contribute significantly to morbidity in transplant recipients.¹⁹ Common side effects include acne, increased appetite and associated weight gain, mood changes, diabetes, hypertension, and impaired wound healing.

One of the most common maintenance immunosuppressive regimens consists of triple-drug therapy: prednisone, a calcineurin inhibitor, and an antimetabolite. Large doses of steroids are usually given perioperatively and in the immediate postoperative period. Protocols vary by center, but the steroid dose is usually tapered to an adult dose of roughly 5 to 15 mg daily, or completely stopped at some point. Steroids are substrates for CYP3A4, CYP3A5, and P-glycoprotein pathways where drug interactions might need to be monitored.^{20,21}

Azathioprine

An antimetabolite, azathioprine (AZA) is converted to 6-mercaptopurine and inhibits both the de novo purine synthesis and salvage purine synthesis. AZA decreases T-lymphocyte activity and decreases antibody production. It has been used in transplant recipients for more than 40 years, but became an adjunctive agent after the introduction of cyclosporine. With the development of newer agents such as MMF, the use of AZA has

decreased significantly. However, it is preferred in recipients who are considering conceiving a child, because MMF is teratogenic in females and can cause birth defects. AZA might be an option for recipients who cannot tolerate the gastrointestinal (GI) side effects of MMF.

The most significant side effect of AZA, often dose-related, is bone marrow suppression. Leukopenia is often reversible with dose reduction or temporary cessation of the drug. Other significant side effects include hepatotoxicity, pancreatitis, neoplasia, anemia, and pulmonary fibrosis. Its most significant drug interaction is with allopurinol, which blocks AZA's metabolism, increasing the risk of pancytopenia. Recommendations are to not use AZA and allopurinol together, or if doing so is unavoidable, to decrease the dose of AZA by 75%.²²

Mycophenolate Mofetil

Approved in May 1995 by the U.S. Food and Drug Administration (FDA) for preventing acute rejection after kidney transplants, MMF has now been incorporated into routine maintenance regimens after many solid organ transplants. Mycophenolate is the prodrug of mycophenolate acid, derived from *Penicillium* fungi. Mycophenolate acid is an inhibitor of inosine monophosphate dehydrogenase (IMPDH) involved in

the de novo pathway of purine synthesis.²³ MMF is available in capsules (250 and 500 mg); the starting dose is 1 g twice daily. In hopes of decreasing the GI side effects, an enteric-coated formulation called Myfortic was developed; its benefits have not been clearly demonstrated in studies, but in some conversion studies, patients did report less GI intolerance. The pharmacokinetics of MMF are complex; mycophenolic acid (MPA) levels are not routinely performed at most transplant centers. Studies have shown that MPA levels and the incidence of rejection are not significantly correlated.²⁴ The most common side effects of MMF are GI in nature, most commonly diarrhea, nausea, dyspepsia, and bloating. Esophagitis and gastritis occur in roughly 5% of recipients and may represent a cytomegalovirus (CMV) or herpesvirus family infection. The other important side effects are leukopenia, anemia, and thrombocytopenia (Table 11-4). Leukopenia can sometimes be reversed by lowering the MMF dose and discontinuing other agents like valganciclovir. MMF does not have any significant drug interactions, but clinicians should be careful to avoid

additive toxicities with other medications that might lead to leukopenia and thrombocytopenia.

Sirolimus

The first mammalian target of rapamycin (mTOR) inhibitors to enter clinical use was sirolimus (Rapamune). A key regulatory kinase, mTOR changes cells from the G1 to S phase in the cell cycle, in response to proliferation signals provided by cytokines like IL-2. The mTOR inhibitors bind to FK506-binding protein (FKBP), and the sirolimus-FKBP complex binds to mTOR. Sirolimus also inhibits proliferation of vascular smooth muscle cells, possibly easing the vasculopathy and progressive fibrosis that can affect allografts. Sirolimus is a substrate for CYP3A4/4 and has many significant drug interactions (see Table 11-4).

To date, sirolimus has been used in a variety of combinations for maintenance immunosuppression, alone or in conjunction with one of the calcineurin inhibitors. In such combinations, sirolimus usually is used to help withdraw, or completely avoid the use of, steroids. It also has been used as an alternative to

Table 11-4

Side effects and drug interactions of the main immunosuppressive drugs

	COMMON SIDE EFFECTS	OTHER MEDICATIONS THAT INCREASE BLOOD LEVELS	OTHER MEDICATIONS THAT DECREASE BLOOD LEVELS	OTHER MEDICATIONS THAT POTENTIATE TOXICITY
Cyclosporine (CSA)	Hypertension, nephrotoxicity, hirsutism, neurotoxicity, gingival hyperplasia, hypomagnesemia, hyperkalemia	Verapamil, diltiazem, clarithromycin, azithromycin, erythromycin, azole antifungals, protease inhibitors, grapefruit juice	Isoniazid, carbamazepine, phenobarbital, phenytoin, rifampin, St. John's Wort	Nephrotoxicity: ganciclovir, aminoglycosides, NSAIDs, ACE-Is, and ARBs
Tacrolimus (FK506)	Hypertension, nephrotoxicity, alopecia, hyperglycemia, neurotoxicity, hypomagnesemia, hyperkalemia	Verapamil, diltiazem, clarithromycin, azithromycin, erythromycin, azole antifungals, protease inhibitors, grapefruit juice	Isoniazid, carbamazepine, phenobarbital, phenytoin, rifampin, St. John's wort	Nephrotoxicity: ganciclovir, aminoglycosides, NSAIDs, ACE-Is, and ARBs
Sirolimus	Thrombocytopenia and neutropenia, elevated cholesterol, extremity edema, impaired wound healing	Verapamil, diltiazem, clarithromycin, azithromycin, erythromycin, azole antifungals, protease inhibitors, grapefruit juice	Isoniazid, carbamazepine, phenobarbital, phenytoin, rifampin, St. John's wort	—
Mycophenolate mofetil	Leukopenia, thrombocytopenia, GI upset	—	Cholestyramine, antacids	Bone marrow suppression: valganciclovir, ganciclovir, TMP-SMX
Corticosteroids	Hyperglycemia, osteoporosis, cataracts, myopathy, weight gain	—	—	—
Azathioprine	Leukopenia, anemia, thrombocytopenia, neoplasia, hepatitis, cholestasis	—	—	Bone marrow suppression: allopurinol, sulfonamides

ACE-I = angiotensin-converting enzyme inhibitor; ARB = angiotensin receptor blocker; NSAID = nonsteroidal anti-inflammatory drug; TMP-SMX = trimethoprim-sulfamethoxazole

tacrolimus or cyclosporine, in a calcineurin-sparing protocol. One of the most significant side effects of sirolimus is hypertriglyceridemia, a condition that may be resistant to statins and fibrates. Impaired wound healing (immediately posttransplant in particular), thrombocytopenia, leukopenia, and anemia also are associated with sirolimus, and these problems are exacerbated when it is used in combination with MMF.^{25,26}

Cyclosporine

The introduction of cyclosporine in the early 1980s dramatically altered the field of transplantation by significantly improving outcomes after kidney transplantation. Cyclosporine binds with its cytoplasmic receptor protein, cyclophilin, which subsequently inhibits the activity of calcineurin, thereby decreasing the expression of several critical T-cell activation genes, the most important being for IL-2. As a result, T-cell activation is suppressed.²⁷

Many formulations of cyclosporine exist, so it is important to know which one the transplant recipient is taking. Sandimmune, an older, oil-based formulation, has poor bioavailability and variable absorption. The newer formulations, Gengraf and Neoral, are microemulsified with improved bioavailability. Cyclosporine can be given intravenously or orally to maintain trough levels of 250 to 350 ng/mL for the first 3 months posttransplant; then it can be tapered to 150 to 250 ng/mL.²⁸

The metabolism of cyclosporine is via the cytochrome P450 system, resulting in many significant drug interactions (see Table 11-4). Calcineurin inhibitors are nephrotoxic and constrict the afferent arteriole in a dose-dependent, reversible manner (Table 11-5). They also can cause hyperkalemia and hypomagnesemia. Several neurologic complications, including headaches, tremor, and seizures, also have been reported.²⁹

Cyclosporine has several undesirable cosmetic effects, including hirsutism and gingival hyperplasia. It is associated with a higher incidence of hypertension and hyperlipidemia than is tacrolimus.

Tacrolimus

The calcineurin inhibitor tacrolimus (Prograf) is now the backbone of most immunosuppressive regimens. Tacrolimus

acts by binding FKBP, causing roughly 10 to 100 times more potent inhibition of IL-2 production than cyclosporine (which acts by binding cyclophilins). It can be given intravenously, orally, or sublingually to maintain trough levels of 8 to 12 ng/mL for the first 3 months posttransplant; then it can be tapered to 6 to 10 ng/mL.

The metabolism of tacrolimus is via the cytochrome P450 system, resulting in many significant drug interactions (see Table 11-4).

Tacrolimus causes a higher incidence of new-onset diabetes posttransplant than does cyclosporine. Other side effects include alopecia, nephrotoxicity, neurotoxicity, hypertension, hyperkalemia, hypomagnesemia, and an increased incidence of certain types of infection.³⁰

Belatacept

The best-characterized pathway of T-cell costimulation includes CD28; its homologue, the cytotoxic T-lymphocyte-associated protein 4 (CTLA4); and their ligands, CD80 and CD86. Belatacept (also known as LEA29Y) was developed through two amino acid substitutions to abatacept (also known as CTLA4-Ig), a fusion protein consisting of the extracellular domain of CTLA4 and the Fc domain of immunoglobulin G (IgG). It is a high-avidity molecule with slower dissociation rates.

Recent trials have compared the use of belatacept vs. a standard cyclosporine protocol in recipients of living donor, deceased donor, and extended-criteria donor kidneys. Belatacept was not inferior to cyclosporine in both patient and allograft survival rates, but was associated with a higher rate of biopsy-proven acute cellular rejection.

In terms of adverse effects, belatacept differs from standard calcineurin-based regimens because of an increased risk of posttransplant lymphoproliferative disorder (PTLD); the greatest risk is in recipients who are Epstein-Barr virus (EBV)-seronegative pretransplant. The FDA recommends the use of belatacept only in seropositive recipients. Studies in liver transplant recipients were halted early because of increased mortality rates.

However, belatacept does have a lower incidence of cardiovascular risk factors including metabolic lipid disorders, hypertension, neurotoxicity, glucose abnormalities, and adverse cosmetic effects. Except for the increased risk of malignancy, the more favorable adverse effect profile of belatacept and its convenient monthly dosing schedule may make it an attractive option for maintenance of immunosuppression, possibly improving compliance.^{31,32}

HUMORAL REJECTION

Rituximab

A chimeric anti-CD20 (anti-B cell) monoclonal antibody, rituximab is currently FDA approved for treating lymphoma. The CD20 antigen is expressed early in the B-cell cycle but is absent on mature plasma cells. The variable region binds to CD20 through three different mechanisms: (a) antibody-dependent cell cytotoxicity, (b) complement-dependent cell killing, and (c) induction of apoptotic cell death. The use of rituximab has grown to include the treatment of antibody-mediated rejection and use in desensitization protocols. Studies so far have been small, with rituximab usually used in conjunction with plasmapheresis, steroids, and intravenous immunoglobulin (IVIG).³³⁻³⁵

Table 11-5

Drug interactions and side effects associated with calcineurin inhibitors

INTERACTIONS	MEDICATIONS
Inhibition of metabolism	Clarithromycin, erythromycin, azole antifungals, diltiazem, verapamil, nicardipine, amiodarone, grapefruit juice, ritonavir, azithromycin
Induction of metabolism	Nevirapine, rifampin, St. John's wort, carbamazepine, phenobarbital, phenytoin, caspofungin
Hyperkalemia	Potassium-sparing diuretics, angiotensin-converting enzyme inhibitors (ACE-Is), angiotensin receptor blockers (ARBs), β -blockers, trimethoprim-sulfamethoxazole
Nephrotoxicity	Nonsteroidal anti-inflammatory drugs, aminoglycosides, amphotericin, ACE-Is, ARBs

Bortezomib

A proteasome inhibitor, bortezomib is FDA approved for treating multiple myeloma. It can directly target plasma cells. Traditional treatments have been successful in removing antibodies, inhibiting antibody activity, or lowering antibody production; however, targeting mature antibody production in plasma cells has not met with success. Bortezomib has been shown to cause apoptosis of normal plasma cells, thereby decreasing alloantibody production in sensitized patients. Several case reports and series have described the use of bortezomib for the treatment of antibody-mediated rejection and in desensitization protocols.^{34,36,37}

Eculizumab

A humanized monoclonal antibody with high affinity for C5, eculizumab is a first-in-class, FDA-approved agent for treating paroxysmal nocturnal hemoglobinuria and hemolytic uremic syndrome. It blocks the activation of the terminal complement cascade. Most antibody-mediated rejection episodes are associated with early complement activation as evidenced on renal transplant biopsies by the presence of C4d+ staining of the peritubular capillaries. Given its highly selective mechanism of action, this agent is predicted to be useful to treat antibody-mediated rejection and to desensitize patients pretransplant. However, its serious adverse effects include an increased risk of infections, especially due to encapsulated bacteria such as *Neisseria meningitidis*. Patients should be immunized with meningococcal vaccine at least 2 weeks before the administration of eculizumab.^{34,38,39}

INFECTIONS AND MALIGNANCIES

Advances in immunosuppression have led to improved graft survival rates. However, the growing population of immunosuppressed patients, in turn, has led to an increased incidence of opportunistic infections and malignancies. Such posttransplant complications have become important barriers to long-term disease-free survival.

Infections

Transplant recipients are predisposed to a variety of infections. Immunosuppression is the obvious reason. Moreover, such patients have already endured end-stage organ disease pretransplant and then the stress of an invasive transplant operation. Posttransplant, they continue to have significant comorbid conditions.

Early. Early infections (i.e., infections occurring within 1 month posttransplant) can be due to a wide spectrum of pathogens (bacterial, viral, and fungal). In the immediate postoperative period, recipients are significantly compromised from the stress of the operation, from induction immunosuppression, and often from initially impaired graft function. Infections during this period can be devastating.

It is imperative to differentiate between medical and surgical infections. Surgical infections are the most common and require expedient surgical intervention. Typical examples include generalized peritonitis, intra-abdominal abscesses, and wound infections.

In liver and pancreas recipients, surgical infections are most severe. The incidence of intra-abdominal infections is decreasing, but they remain a significant problem: they are the second most common reason (after vascular thrombosis) for graft loss in pancreas recipients.

Lengthy operations with significant blood loss, prolonged warm and cold ischemic times, and spillage of contaminated fluid (bile, urine, or bowel contents) predispose patients to intra-abdominal infections. Other prominent risk factors are the high level of induction immunosuppression immediately posttransplant and anastomotic leaks. Furthermore, pretransplant infections can re-emerge or worsen.

The signs and symptoms of intra-abdominal infections are those of peritonitis: fever, hypotension, ileus, and abdominal pain, although the latter can be masked by immunosuppression. Treatment entails a prompt return to the operating room. Intra-abdominal infections are usually polymicrobial, involving several bacterial and fungal species. Common bacterial isolates include *Escherichia coli*, as well as *Enterococcus*, *Klebsiella*, and *Pseudomonas* species. Common fungal isolates are *Candida albicans*, *Candida krusei*, and *Candida glabrata*. Localized infections or abscesses can be treated with percutaneous drainage and antibiotics.

Medical infections include respiratory, urinary tract, and bloodstream infections. Medical treatment should also be aggressive, often including empiric antibiotics and antifungal medications even before culture results are available. Recipients of organs from infected donors should be treated per the results of donor culture speciation and the antibiotic sensitivity profile.

Late. Late infections primarily are due to chronic immunosuppression, specifically the depression of cell-mediated immunity that renders recipients susceptible to viruses, fungi, and parasites.

Members of the herpesvirus group are the most common etiologic agents of viral infections posttransplantation, with herpes simplex virus (HSV), CMV, and EBV being the most prominent. Pretransplant exposure to viruses may confer immunity. Recipients who are seronegative for HSV, CMV, and/or EBV have a higher incidence of posttransplant infections, especially if they receive donor allografts from seropositive donors.

CMV is a latent infection that can be transmitted to seronaive recipients by donor organs from seropositive individuals, can reactivate during immunosuppression, or both. Infections usually occur 3 to 6 months posttransplant or during treatment for rejection. The incidence of CMV has been greatly reduced with 12-week acyclovir prophylaxis.⁴⁰ CMV infections range from an asymptomatic or mild flu-like syndrome to tissue-invasive disease resulting in pneumonitis, hepatitis, and GI ulcerations. Symptomatic infections and all tissue-invasive CMV disease should be treated with intravenous (IV) ganciclovir, a reduction in immunosuppression, or both, although successful treatment of mild to moderate rejection and concurrent mild to moderate CMV disease has been described.

EBV infections range from a mild mononucleosis syndrome to severe hepatitis and highly morbid PTLD. PTLD ranges from a localized tumor to a progressive, diffuse infiltration of various organs including the brain. It results from the proliferation of EBV-positive B cells in immunosuppressed patients. The main risk factors are a high degree of immunosuppression and a predisposing EBV serostatus (seronaive recipient, seropositive donor). Among patients with early lesions, the first line of treatment is to reduce immunosuppression. For those with more advanced PTLD, rituximab is used.

After 6 months posttransplant, the risk of invasive fungal infections is closely associated with environmental exposures. *Blastomyces dermatitidis* grows in moist soil in the Midwest and Southeast regions of the United States. Diagnosis is confirmed by biopsy; the preferred treatment is IV amphotericin B.

Coccidioides immitis can cause invasive coccidioidomycosis after inhalation of aerosolized infectious particles. It is endemic in the Southwest, Northern Mexico, and various parts of Central and South America. This infection can be resilient and difficult to treat. The first line of treatment is high-dose amphotericin B.

Histoplasma capsulatum is found in chicken and bat droppings in the Ohio River and Mississippi River valleys. Dissemination is commonplace; up to a quarter of patients have central nervous system (CNS) involvement. Treatment consists of prolonged (3 to 13 months) administration of oral itraconazole.

Opportunistic infections with *Aspergillus*, *Cryptococcus*, *Mucor*, and *Rhizopus* species are rare but can cause serious infections. Patients with invasive *Candida* or *Aspergillus* infections have a 20% mortality rate. Prophylaxis with fluconazole has been shown to reduce invasive fungal infections in liver recipients.⁴¹

Pneumocystis jiroveci (also known as PCP) is ubiquitous and can cause pulmonary disease in immunocompromised patients. However, trimethoprim-sulfamethoxazole (TMP-SMX) is effective prophylaxis against PCP, and daily, lifelong administration has virtually eliminated this infection among transplant recipients.

Malignancies

Chronic immunosuppression increases the risk of developing certain types of malignancies. The most extensive data, from a cohort study involving more than 175,000 solid organ transplant recipients, showed that 10,656 of them developed malignancies. The standardized incidence ratio was 2.10 (as compared with the general population). Recipients had at least a fivefold increase (as compared with the general population) in these types of malignancies: Kaposi's sarcoma, nonmelanoma skin cancer, non-Hodgkin's lymphoma, and cancer of the liver, anus, vulva, and lip. In addition, recipients had a statistically significant increase (as compared with the general population) in melanoma, Hodgkin's lymphoma, and cancer of the lung, kidney, colon, rectum, and pancreas.⁴²

ORGAN PROCUREMENT AND PRESERVATION

Organ procurement is a key element in organ transplantation. Currently, 58 organ procurement organizations (OPOs) exist in the United States, all members of the Organ Procurement and Transplantation Network (OPTN), which is a federally mandated network created by and overseen by UNOS. Each OPO is responsible for evaluating and procuring deceased donor organs for transplantation in a specific geographic region. Hospitals receiving any type of federal reimbursement for their services (whether transplant-related or not) are required to report all deaths to their OPO in a timely manner. Each OPO then determines the medical suitability of the deceased for organ donation; requests consent for donation from family members; if consent is given, contacts the OPTN to analyze and identify potential recipients whose HLA antigens most closely match those of the donor; and arranges for the recovery and transport of any donated organs.

Strategies to increase organ donation and utilization have been successfully implemented in the last 10 years. The nationwide "Organ Donation Breakthrough Collaborative," sponsored by the U.S. Department of Health and Human Services in 2003, brought the OPOs and transplant communities into a single

concerted program to develop best practices guidelines. However, a severe donor shortage remains. The number of living organ donors peaked in 2007 and has declined since.

Alternative options include tissue engineering and stem cell research, but those fields are in their infancy in terms of producing fully functional and vascularized human organs. With the development of genetic knockout pigs, xenotransplantation still shows promise, but two problems in particular—immunologic barriers and xenosis (also known as zoonosis) of endogenous porcine retroviruses—have yet to be satisfactorily addressed.

Today, the gap between patients waiting for organ transplants and the number of organs available continues to widen. More than 110,000 patients are on the waiting list for solid organ transplants, but only 28,456 transplants were performed in 2011.

Deceased Donors

Most transplants today utilize organs from deceased donors. Formerly, death was determined by the cessation of both cardiac and respiratory function.

Donation after Brain Death. In 1968, the concept of "irreversible coma" was introduced by an ad hoc committee report at Harvard Medical School; that concept was pivotal to the final acceptance, in 1981, of "brain death" as a legal definition in the United States. The legal language states that the declaration of brain death should be in accordance with acceptable medical standards, but does not specify clinical methodology. It is customary for hospitals to establish their own policies to declare brain death, according to their standards of care and local regulations.

Typically, brain death is defined as the irreversible cessation of brain function, including the brainstem. The presence of medical conditions that mimic brain death—such as drug overdose, medication side effects, severe hypothermia, hypoglycemia, induced coma, and chronic vegetative state—need to be excluded. The latest evidence-based guideline on determining brain death in adults reaffirmed the validity of current clinical practice.⁴³ Briefly, the clinical diagnosis of brain death consists of four essential steps: (a) establishment of the proximate cause of the neurologic insult; (b) clinical examinations to determine coma, absence of brainstem reflexes, and apnea; (c) utilization of ancillary tests, such as electroencephalography (EEG), cerebral angiography, or nuclear scans, in patients who do not meet clinical criteria; and (d) appropriate documentation. A similar guideline on determining brain death in pediatric patients was recently developed.⁴⁴

Once the diagnosis of brain death has been established, the local OPO assumes the care of the potential donor and initiates the process of donor evaluation and organ donation, and the potential donor is screened for contraindications to donation. The medical history and social history are obtained from the available family members. A battery of tests, including serologic or molecular detection of human immunodeficiency virus (HIV) and viral hepatitis, are performed. The exact medical conditions that preclude donation vary; nonetheless, in the United States, infections and other medical conditions that determine eligibility are dictated by UNOS bylaws and routinely reviewed and updated.

The OPO focuses on preserving organ function and optimizing peripheral oxygen delivery until organ procurement commences.⁴⁵ In all deceased donors, core temperature, systemic arterial blood pressure, arterial oxygen saturation, and urine output must be determined routinely and frequently. Arterial blood gases, serum electrolytes, blood urea nitrogen,

serum creatinine, liver enzyme, hemoglobin, and coagulation tests need to be monitored regularly. In all brain-dead donors, elevated intracranial pressure triggers a compensatory catecholamine response to maintain cerebral perfusion pressure. Ischemic injury to the spinal cord and the sympathetic system may lead to a profound vasodilation. As a result, brain-dead donors frequently have severe hemodynamic and metabolic derangements, so aggressive monitoring and intervention are required to prevent loss of precious organs.

Previous studies of deceased donor care focused on organ-specific resuscitation protocols that resulted in only marginal gains in the number of organs transplanted. The latest developments center on multisystem protocols to increase the number of organs transplanted per donor (OTPD).^{46,47} The goals are to maintain a core temperature between 36.0 and 37.5°C, a mean arterial pressure >70 mmHg or a systolic pressure >100 mmHg, and a hemoglobin level between 7 and 10 g/dL; hormonal therapy and aggressive treatment of arrhythmias and metabolic derangements are also called for.⁴⁷

Surgical Technique. Procurement of multiple organs (heart, lungs, kidney, liver, pancreas, and/or small bowel), or multivisceral procurement, was first described by the Pittsburgh group in 1987.⁴⁸ Since then, most centers have incorporated changes, especially with regard to the timing and location of dissection and flushing.^{49,50} The basic steps involve a long incision to provide wide exposure of all thoracic and abdominal organs (Fig. 11-3). A Cattell-Braasch maneuver (complete mobilization of the distal small bowel, right colon, and duodenum) is performed to allow for identification of the distal aorta, iliac bifurcation, and distal inferior vena cava (IVC). The infrarenal aorta is the site for inserting the cannula that will allow for flushing of the organs with cold preservation solution. Sometimes, division of the inferior mesenteric artery is necessary to facilitate the exposure of the distal aorta. The third portion of the duodenum is retracted cephalad to expose the root of the superior mesenteric artery (SMA). Limited dissection is performed at the root of the SMA, which is encircled with a vessel loop to enable its temporary occlusion at the time of flushing, thus reducing the incidence of overperfusion injury to the pancreas.

A large anomalous or replaced right hepatic artery typically rises from the SMA, and this should be identified and

preserved. Lateral to the SMA is the inferior mesenteric vein (IMV), which can be cannulated for portal flushing. Dissection of the hepatic hilum and the pancreas should be limited to the common hepatic artery (CHA), and branches of the CHA (e.g., splenic, left gastric, and gastroduodenal arteries) are exposed. The gastrohepatic ligament is carefully examined to preserve a large anomalous or replaced left hepatic artery, if present. The supraceliac aorta can be exposed by dividing the left triangular ligament of the liver and the gastrohepatic ligament.

The common bile duct is transected at the superior margin of the head of the pancreas. The gallbladder is incised and flushed with ice-cold saline to clear the bile and sludge. If the pancreas is to be procured, the duodenum is flushed with antimicrobial solution. Before the cannulation of the distal aorta, systemic heparinization (300 units/kg) is administered. The supraceliac aorta is clamped; cold preservation fluid is infused via the aortic (systemic) and IMV (portal) cannulas. The thoracic organs, liver, pancreas, and kidneys are then removed.

Donation after Cardiac Death. Given the severe shortage of donor organs, donation after cardiac death (DCD)—also known as donation by non-heart-beating donors (NHBDs)—was reintroduced to the transplant community in the 1990s.⁵¹ The category of DCD (Maastricht classification) was initially proposed at an international workshop and is now widely adopted for organ procurement.⁵² Currently, most NHBDs in the United States meet Maastricht classification III; that is, they have suffered a devastating injury with no chance of a meaningful recovery but do not meet the criteria for brain death. After consent for donation is obtained from the next of kin, the donor's life support is removed. After the cessation of cardiac and respiratory function, organ procurement commences. DCD procurement protocols vary between states; religious and cultural differences need to be taken into consideration. The surgical team must be familiar with, and respect, the local protocol.

With cardiac death (as opposed to brain death), warm ischemic injury to organs can occur during the period between circulatory cessation and rapid core cooling through perfusion of preservation solution. However, the difference in long-term outcomes is negligible for recipients of organs from either type of donor. Still, a significant percentage of liver grafts procured after cardiac death, especially those with more than 25 minutes of warm ischemic time, develop devastating ischemic cholangiopathy and fail.⁵³

A new development to minimize ischemic injury to organs procured after cardiac death has been the application of extracorporeal membrane oxygenation (ECMO). With ECMO, DCD differs in two key ways: (a) cannulation occurs *before* withdrawal of life support and (b) organs are perfused via ECMO with warm oxygenated blood *after* declaration of cardiac death. The initial experience with organs procured using ECMO has been encouraging.

Surgical Technique. Surgeons who perform multiple organ retrieval should be familiar and experienced with the super-rapid technique described by the Pittsburgh group.⁵⁴ Preferably, NHBDs undergo withdrawal of life support in the operating room *after* the surgical site is prepped and draped, as soon as the surgical team is ready. Alternatively, the NHBD is transported to the operating room after declaration of cardiac death.

A midline incision is used to rapidly gain entry into the abdominal cavity. An assistant retracts the small bowel and the sigmoid colon laterally, so that the bifurcation of the aorta can

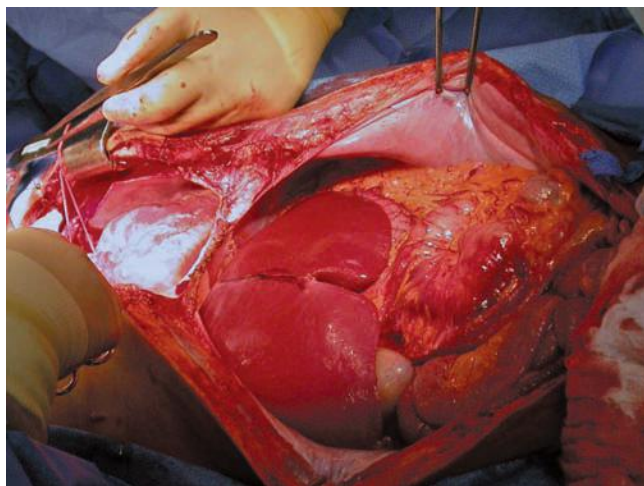


Figure 11-3. Exposure for thoracic and abdominal organ procurement.

be easily identified on the left side of the vertebral column. A short segment of the distal aorta is dissected out from the retroperitoneum. A moist umbilical tape is passed around the aorta, which is used to secure a cannula. The distal aorta is clamped. Next, a cannula is passed cephalad through an aortotomy and secured. Flushing with cold preservation solution is started at once, followed by cross-clamping the aorta proximally (thoracic aorta) and venting through the vena cava. The portal flush is then instituted.

The rest of the procedure is similar to procurement after brain death, with two noticeable differences. First, to avoid injury to a large anomalous or replaced left hepatic artery, the gastrohepatic ligament and the left gastric artery are separated from the stomach at the lesser curvature. Second, to avoid injury to a large anomalous or replaced right hepatic artery, the SMA is examined before it is divided. If the pancreas is not procured, a common aortic patch encompassing both the SMA and the celiac artery can be procured with the liver.

Living Donors

The maxim of medical ethics is “*primum non nocere*” (above all, do no harm), and for that reason, living organ donation presents unique ethical and legal challenges. Performing potentially harmful operations to remove organs from healthy individuals seems, at first glance, to contradict that maxim. But in fact, the ethical framework of living organ donation rests on three guiding principles respected in all discussions of medical practice: *beneficence* to the recipient, *nonmaleficence* to the donor, and the donor’s *right to autonomy*.⁵⁵ In order to achieve optimal outcomes (the common good), transplant professionals should focus on maximizing the benefits for the recipient and minimizing the damage to the donor. The Uniform Anatomical Gift Act adopted by all states in the United States (with slight variations) provides the legal framework for competent adult living donors to decide whether or not to donate. It is the fiduciary duty of transplant professionals to explain the risks of organ donation. Any decision to donate should be uncoerced, and no enticements should be offered.

The use of living donors offers numerous advantages for recipients in need. First and foremost is the availability of lifesaving organs for those who would otherwise succumb to the progression of their end-stage disease. In certain parts of the world, such as East Asia, the concept of brain death and the use of deceased donors conflict with the prevailing culture or religion. Even in countries where the use of deceased donors is accepted, the use of living donors may significantly shorten the waiting time for recipients. A shorter waiting time generally implies a healthier recipient—one whose body has not been ravaged by prolonged end-stage organ failure. Moreover, with the use of living donors, transplants are planned (rather than emergency) procedures, allowing for better preoperative preparation of the recipient. Receiving an organ from a closely matched relative may also have immunologic benefits. And long-term results may be superior with the use of living donors, as is certainly the case with kidney transplants.

The major disadvantage is the risk to the living donor. Medically, there is no possibility of benefit to the donor, only the potential for harm. The risk of death associated with donation depends on the organ being removed. For a nephrectomy, the estimated mortality risk is less than 0.05%; for a partial hepatectomy, about 0.2%. The risk of surgical and medical complications also depends on the procedure being performed.

In addition, long-term complications may be associated with a partial loss of organ function after donation. The guiding principle should be minimization of risk to the donor. All potential risks must be carefully explained to the potential donor, and written informed consent must be obtained.⁵⁶

Surgical Technique. The kidney, the first organ to be transplanted from living donors, is still the most common organ donated by these individuals. The donor’s left kidney is usually preferable because of the long vascular pedicle. Use of living donor kidneys with multiple renal arteries should be avoided, in order to decrease the complexity of the vascular reconstruction and to help avoid graft thrombosis. Most donor nephrectomies are now performed via minimally invasive techniques, that is, laparoscopically, whether hand-assisted or not. With laparoscopic techniques, an intraperitoneal approach is most common: it involves mobilizing the colon, isolating the ureter and renal vessels, mobilizing the kidney, dividing the renal vessels and the distal ureter [C6], and removing the kidney (Fig. 11-4). Extensive dissection around the ureter should be avoided, and the surgeon should strive to preserve as much length of the renal artery and vein as possible.

Liver transplants with living donors are not as commonly performed, given the significantly higher rates of donor mortality and morbidity. Initially, only adult donors for pediatric recipients were selected, but now, living donor liver transplants also involve adult donors for adult recipients. In dual graft living donor liver transplants, segmental grafts from two living donors augment the recipient’s graft size.⁵⁷ The donor hepatectomy is similar to a major lobar hepatectomy, except that it is important to preserve the integrity of the vascular structure until graft resection (Fig. 11-5).

Living donor transplants of organs other than the kidney and liver are fairly uncommon, but certain centers do perform such transplants. Living donor pancreas transplants involve performing a distal pancreatectomy, with the graft consisting of the body and tail of the pancreas; vascular inflow and outflow are provided by the splenic artery and splenic vein. Living donor intestinal transplants usually involve removal of about 200 cm of the donor’s ileum, with inflow and outflow provided by the ileocolic vessels. Living donor lung transplants involve removal of one lobe of one lung from each of two donors; both grafts are then transplanted into the recipient.

Organ Preservation

The development and continuing refinement of organ preservation methods have completely revolutionized the transplant field. Extending the time that organs can be safely stored after procurement has enabled better organ utilization and better recipient outcomes.^{58,59} Hypothermia and pharmacologic inhibition are the two most frequent methods. Both slow—yet cannot completely shut down—the removed organ’s metabolic activity, so both have adverse effects, such as cellular swelling and degradation. Cold storage solutions were introduced to mitigate some of the adverse effects of hypothermia or pharmacologic inhibition alone. Such solutions help prevent cellular swelling and the loss of cellular potassium.

One, and perhaps the most effective, preservation solution was developed at the University of Wisconsin and remains in wide use.⁶⁰ Its ingredients include lactobionate (which helps prevent cellular swelling and reperfusion injury), raffinose, and hydroxyethyl starch (which helps reduce swelling of endothelial

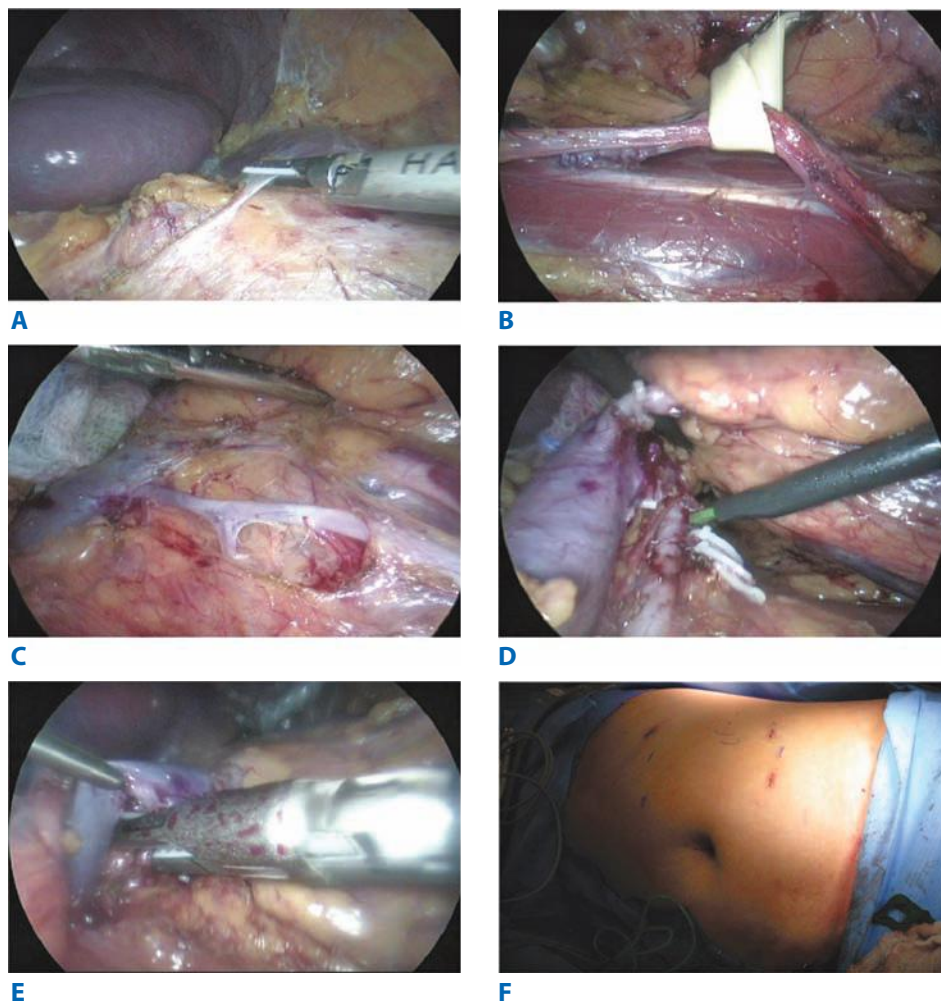


Figure 11-4. Laparoscopic left donor nephroureterectomy. **A.** Takedown of splenic flexure of colon to expose the left renal hilum. **B.** Dissection of left ureter off the psoas muscle. **C.** Dissection of left renal vein and gonadal vein. Left ureter seen lateral to the dissection. **D.** Dissection of left renal artery. Lumbar veins clipped and divided. **E.** Endo-TA stapler transection of the left renal artery. **F.** Placement of ports and Pfannenstiel incision for the donor kidney extraction.

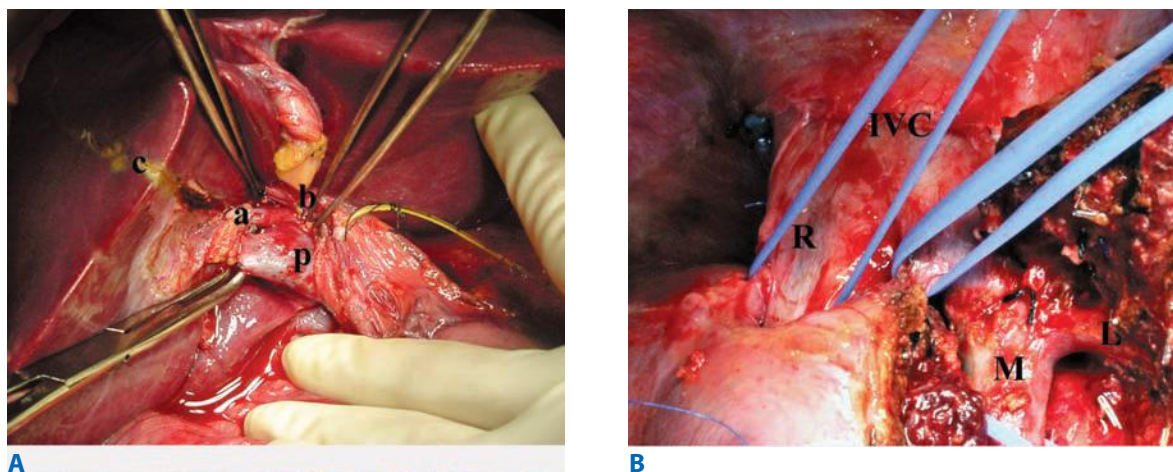


Figure 11-5. Donor hepatectomy (right hepatectomy). **A.** The liver parenchymal transection line (c, the Cantlie line) marked with cautery. Right portal vein (p) and right hepatic artery (a) isolated. b = bile duct. Cystic duct was cannulated for intraoperative cholangiography. **B.** Exposure of hepatic veins after transection of the parenchyma. IVC = inferior vena cava; L = left hepatic vein; M = middle hepatic vein; R = right hepatic vein

cells, thereby decreasing edema). Histidine-tryptophan-ketoglutarate solution is also currently in wide use.⁶¹

Despite enhancements in preservation methods, the amount of time that an organ can be safely stored remains relatively short (hours, not days), particularly with organs from marginal donors. Among kidney recipients, delayed graft function becomes significantly more frequent after cold ischemic times of more than 24 hours, necessitating temporary dialysis, which is associated with increased risks of graft loss and higher costs.⁶² Among liver recipients, primary nonfunction and biliary complications ensue after prolonged cold ischemic times. In the case of heart and lung recipients, ischemic times should be under 6 hours. All of those times assume the use of normal donors.

There is revived interest in the use of the pulsatile perfusion pump, a kidney graft preservation method that has been available for more than 40 years.⁶³ With the increasing shortage of available donor organs and the rise in the use of organs after cardiac death, the pulsatile perfusion pump is garnering renewed enthusiasm as an adjunct method of preservation, even for donor organs other than kidneys.^{64,65}

KIDNEY TRANSPLANTATION

Introduction

Ullman reported the first attempted human kidney transplant in 1902.⁶⁶ For the next 50 years, sporadic attempts all ended in either technical failure or in graft failure from rejection. Joseph Murray performed the first successful kidney transplant in 1954, an epochal event in the history of organ transplantation. In that first case, the immunologic barrier was circumvented by transplanting a kidney between identical twins.⁶⁷ For his pivotal contribution, Murray shared the Nobel Prize in Physiology or Medicine in 1990 with E. Donnall Thomas for their discoveries concerning “organ and cell transplantation in the treatment of human disease.”

The introduction of AZA (Imuran) in 1960 marked the beginning of a new era in kidney transplantation. With the combination of steroids and AZA for maintenance immunosuppression, the 1-year graft survival rate with a living related donor kidney approached 80%; with a deceased donor kidney, the rate was 65%.⁶⁸ In the ensuing years, major milestones included the introduction of more effective immunosuppressive medications with lower toxicity profiles, such as polyclonal antilymphocyte globulin in the 1970s, cyclosporine in the 1980s, tacrolimus in the 1990s, and biologics in the first decade of the twenty-first century, as previously mentioned.

Parallel to the developments in medical science were the transplant community's concerted efforts to improve use of healthcare resources. In the United States, the Social Security amendments of 1972 provided Medicare coverage for patients with end-stage renal disease (ESRD). The National Organ Transplant Act of 1984 initiated the process of creating what later became UNOS, an umbrella organization to ensure access to organs by patients in need, to enhance organ procurement and allocation, and to improve posttransplant outcomes. This infrastructure later became the blueprint for other countries to follow. As a result, organ transplantation is the most transparent field of medicine. Data such as transplant center performance are readily available on public websites; penalties for violation of regulations and for underperformance often result in transplant programs being shut down.

Today, a kidney transplant remains the most definitive and durable renal replacement therapy for patients with ESRD. It offers better survival and improved quality of life and is considerably more cost-effective than dialysis.^{69,70} According to the 2010 Scientific Registry of Transplant Recipients (SRTR) annual report, a total of 84,614 adult patients were on the kidney transplant waiting list, including 33,215 added just that year.⁷¹ Yet in 2009, only 15,964 adult kidney transplants were performed in the United States (9912 with a deceased donor and 6052 with a living donor). Of note, the number of patients added to the kidney transplant waiting list has increased every year, but the number of kidney transplants performed has been declining since 2006. On the positive side, posttransplant outcomes have continued to improve: in 2009, the 1-year graft survival rate with a living donor kidney was 96.5%; with a deceased donor kidney, the rate was 92.0%.

The advantages of a living donor kidney transplant include better posttransplant outcomes, avoidance of prolonged waiting time and dialysis, and the ability to coordinate the donor and recipient procedures in a timely fashion. Living donor kidney recipients enjoy better long-term outcomes, a low incidence of delayed graft function, and reduced risks of posttransplant complications. Furthermore, the elective nature of living donor kidney transplants provides unique opportunities for recipient desensitization treatment if the donor and recipient are ABO-incompatible or if the HLA cross-match results are positive.

Some of the challenges transplant professionals face today are closing the growing gap between supply and demand and thereby reducing the current prolonged waiting times; refining immunosuppressive medications to achieve better outcomes with reduced toxicity; and caring for patients who develop rejection, especially antibody-mediated rejection.

Pretransplant Evaluation

Active infection or the presence of a malignancy, active substance abuse, and poorly controlled psychiatric illness are the few absolute contraindications to a kidney transplant. Studies have demonstrated the overwhelming benefits of kidney transplants in terms of patient survival, quality of life, and cost-effectiveness, so most patients with ESRD are referred for consideration of a kidney transplant. However, to achieve optimal transplant outcomes, the many risks (such as the surgical stress to the cardiovascular system, the development of infections or malignancies with long-term immunosuppression, and the psychosocial and financial impacts on compliance) must be carefully balanced.

Any problems detected during the evaluation of transplant candidates are communicated to their referring physician and/or to a specialist if advanced evaluation and treatment are needed, ultimately improving overall care. Essentially, the pretransplant evaluation is a multifaceted approach to patient education and disease management.

Before the pretransplant medical evaluation begins, kidney transplant candidates are encouraged to attend a group meeting focused on patient education. The meeting is coordinated by a transplant physician or surgeon. The intent is to familiarize patients with the pretransplant evaluation process and with pertinent medical concepts and terms. In an open forum format, important decisions such as type of donor (living vs. deceased) are discussed. The group meeting empowers patients to fully participate in their care and serves as an impetus for a meaningful dialogue with healthcare professionals.

Medical Evaluation

Cardiovascular Disease. Diabetes and hypertension are the leading causes of chronic renal disease. Concomitant cardiovascular disease (CVD) is a common finding in this population. An estimated 30% to 42% of deaths with a functioning kidney graft are due to CVD.^{72,73} Therefore, assessment of the potential kidney transplant candidate's cardiovascular status is an important part of the pretransplant evaluation.

In fact, the American Heart Association and the American College of Cardiology Foundation recently published their expert consensus on CVD evaluation and management for solid organ transplant candidates.⁷⁴ The process should focus on careful screening for the presence of significant cardiac conditions (e.g., angina, valvular disease, and arrhythmias) and for a prior history of congestive heart failure, coronary interventions, or valvular surgery. The perioperative risk assessment is based on patient symptoms and exercise tolerance. For all kidney transplant candidates, a resting 12-lead electrocardiogram (ECG) should be obtained. In addition, in this population, the use of echocardiography to analyze left ventricular function and to assess for pulmonary hypertension is useful.

Stress testing may be considered in patients with no active cardiac condition but with risk factors such as diabetes, hemodialysis for more than 1 year, left ventricular hypertrophy, age greater than 60 years, smoking, hypertension, and dyslipidemia. The utility of noninvasive stress testing (as compared with angiographic studies) for evaluating coronary artery disease is controversial; an additional prognostic marker is the troponin T (cTnT) level.

Malignancies. Because of the long-term use of immunosuppressive medications, transplant recipients are at increased risk for development of malignancies. Untreated and/or active malignancies are absolute contraindications to a transplant (with two exceptions: nonmelanocytic skin cancer and incidental renal cell cancer identified at the time of concurrent nephrectomy [i.e., for polycystic kidney disease] and renal transplantation). For most patients who have undergone treatment of low-grade tumors with a low risk of recurrence (e.g., completely locally excised low-grade squamous cell cancer of the skin, colon cancer in a polyp absent stalk invasion), a wait of at least 2 years after successful treatment is recommended before a kidney transplant can be considered. However, for certain types of tumors, especially at advanced stages or those with a high risk of recurrence (e.g., melanoma, lymphoma, renal cell cancer, breast cancer, colon cancer), a delay of at least 5 years is advisable. According to the Israel Penn International Transplant Tumor Registry, tumor recurrence posttransplant is not infrequent: the recurrence rate is 67% in patients with multiple myeloma, 53% in nonmelanocytic skin cancer, 29% in bladder cancer, and 23% in breast cancer.⁷⁵

Infections. A thorough history of infections and immunizations should be obtained from transplant candidates, who need all recommended age-appropriate vaccinations according to the Centers for Disease Control and Prevention (CDC) guidelines. Ideally, vaccinations should be completed at least 4 to 6 weeks before the kidney transplant takes place. Immunosuppressive medications blunt the immune response and reduce the effectiveness of vaccinations; even more important, with attenuated vaccines, vaccine-derived infections could occur. If a splenectomy is anticipated (e.g., in recipients whose donor is ABO-incompatible or whose HLA cross-match results are positive),

then they should be immunized against encapsulated organisms (such as *Neisseria meningitidis*, *Haemophilus influenzae*, and *Streptococcus pneumoniae*) well in advance of the splenectomy.

Transplant candidates should undergo routine tuberculosis (TB) screening. According to the latest CDC report, in 2011, 3929 TB cases were diagnosed in persons born in the United States and 6546 were diagnosed in foreign-born persons.⁷⁶ Serologic screening combined with a chest roentgenogram for fungal infections such as coccidioidomycosis or histoplasmosis, in patients who either have a history of those infections or are from an endemic area, are recommended. Chronic infections such as osteomyelitis or endocarditis must be fully treated; a suitable waiting period after successful treatment must occur, in order to ensure that relapse does not occur.

Hepatitis can be caused by five different types of viruses, hepatitis virus A, B, C, D, and E, with the first three being the most common. Acute viral hepatitis is a contraindication to a kidney transplant; however, chronic viral hepatitis (most commonly caused by hepatitis B [HBV] or C [HCV]) does not preclude a recipient from undergoing a kidney transplant. In such candidates, obtaining a liver biopsy is essential to assess the disease severity. Recipients infected with HBV should undergo antiviral treatment (e.g., lamivudine) to prevent reactivation and progression of liver disease. Note that HBV is a noncytopathic virus; the liver damage is the result of an immune-mediated process.⁷⁷ Moreover, the presence of normal liver enzymes in patients with HBV antigenemia does not predict the severity of parenchymal damage.

Transplant candidates with chronic HCV infection often have HCV-related glomerulonephritis. As with HBV infection, the clinical presentation and biochemical findings with HCV infection are often unreliable in predicting liver damage. In patients with evidence of cirrhosis, a combined liver-kidney transplant should be considered. In appropriate candidates, pretransplant antiviral treatment with interferon- α may be considered. However, after a kidney transplant, interferon treatment is not recommended, because it may precipitate graft rejection.

Thanks to the excellent outcomes of highly active antiretroviral therapy (HAART), infection with HIV is no longer considered a contraindication to a kidney transplant. Kidney transplant candidates with HIV must have an undetectable HIV viral load and a CD4 lymphocyte count greater than 200/mm³; in addition, they must not have had any opportunistic infection in the previous year.⁷⁸

Latent viral infections such as CMV and EBV are of particular interest, given the risks of reactivation posttransplant and the detrimental effects on graft and patient survival. Knowing the serologic status of CMV and EBV infections helps transplant professionals gauge the risk of immunosuppressive regimens and the impact of the donor's viral status, thereby guiding plans for posttransplant antiviral prophylaxis treatment or, as noted earlier, avoiding transplants between a seropositive donor and a seronegative recipient.

Kidney Disease. The third most common cause of graft loss in kidney transplant recipients is recurrence of glomerular diseases such as focal segmental glomerulosclerosis (FSGS), immunoglobulin A (IgA) nephropathy, hemolytic uremic syndrome, systemic lupus erythematosus, and membranoproliferative glomerulonephritis. FSGS deserves special mention for its frequent occurrence and dramatic presentation of early graft loss. An estimated 30% to 40% of FSGS patients develop recurrent disease posttransplant; of those, up to half eventually

lose their graft.⁷⁹ In recipients with a history of FSGS, posttransplant nephrotic proteinuria should be promptly investigated; if diagnosis is confirmed by kidney biopsy, rescue plasmapheresis should be instituted at once. Adjuvant therapy with rituximab recently has been proposed.⁸⁰

Hypercoagulopathy. Kidney transplant candidates with a history of thrombotic events, repeated miscarriages, or a family history of thrombophilia should be screened for the following coagulopathic disorders: activated protein C resistance ratio, factor V Leiden mutation, factor II 20210 gene mutation, antiphospholipid antibody, lupus anticoagulation, protein C or S deficiency, antithrombin III deficiency, and hyperhomocysteinemia. In recipients at risk for hypercoagulopathy, pediatric kidney grafts should be avoided; so should any kidney allografts with a complex vascular anatomy.⁸¹ A perioperative anticoagulation protocol is recommended in this population.

Surgical Evaluation

Urologic Evaluation. Kidney transplant candidates (pediatric patients, in particular) with chronic kidney disease as a result of congenital or genitourinary abnormalities should undergo a thorough urologic evaluation. A voiding cystourethrogram and a complete lower urinary tract evaluation to rule out outlet obstruction are essential. Indications for a native nephrectomy include chronic pyelonephritis, large polycystic kidneys with loss of intra-abdominal domain, significant vesicoureteral reflux, or uncontrollable renovascular hypertension.

Vascular Evaluation. The potential implant sites for a kidney graft include the recipient's aorta, vena cava, and iliac vessels. Careful physical examination often reveals significant central and/or peripheral vascular disease. Findings such as a pulsatile intra-abdominal mass, diminished or absent peripheral pulse, claudication, rest pain, and tissue loss in lower extremities should be further evaluated by abdominal computed tomography scan or ultrasound, Doppler studies, and/or angiography. With the popularity of endovascular interventions, transplant surgeons should also be familiar with such technology and have detailed anatomic studies of patients with vascular stents.

Immunologic Evaluation. ABO blood typing and HLA typing (HLA-A, -B, and -DR) are required before a kidney transplant. The method of screening for preformed antibodies against HLA antigens (because of prior transplants, blood transfusions, or pregnancies) is evolving. The panel-reactive antibody (PRA) assay is a screening test that examines the ability of serum from a kidney transplant candidate to lyse lymphocytes from a panel of HLA-typed donors. A numeric value, expressed as a percentage, indicates the likelihood of a positive cross-match with a donor. A higher PRA level identifies patients at high risk for a positive cross-match and therefore serves as a surrogate marker to measure the difficulty of finding a suitable donor and the risk of graft rejection.

The latest development in anti-HLA antibody screening is Luminex technology, using HLA-coated fluorescent microbeads and flow cytometry. In theory, this technology pinpoints donor-specific antibodies (DSAs) in the serum of a kidney transplant candidate with a high PRA level. Since all organ donors must undergo HLA typing, a negative cross-match for recipients with a high PRA level can be ensured by avoiding the selection of donors carrying unacceptable antigens (i.e., a virtual cross-match).⁸² Kidney transplant candidate data (including ABO blood types, HLA types, and DSAs) are now entered into a

nationwide central database to facilitate deceased donor kidney allocation, as described earlier.

Psychosocial Evaluation. Psychiatric disorders have been recognized as important contributing factors to poor outcomes posttransplant. Patients with uncontrolled psychiatric disorders are at high risk for noncompliance with treatment, impaired cognitive function, and the development of substance abuse. The psychosocial evaluation is essential to ensure that transplant candidates understand the risks and benefits of the procedure and that they adhere to the lifetime immunosuppressive medication regimen.

Recipient Operation

Kidney allografts usually are transplanted heterotopically. The iliac fossa is recognized as the ideal position because of its proximity to the recipient's bladder and iliac vessels.^{83,84}

Retroperitoneal allograft placement also allows easy access for percutaneous biopsies and interventions for ureteral complications. The right iliac fossa is the preferred site because of its easy access to the recipient's iliac vessels. However, if a pancreas transplant is anticipated in the future or if now failed kidney grafts have been placed at the right iliac fossa, then the left iliac fossa is used for implantation. The current surgical technique for kidney transplants was developed and popularized in the 1950s and 1960s and has changed little since.⁸⁵

A large-bore three-lumen urinary catheter is inserted after the recipient is anesthetized, and it is occluded with a clamp beneath the surgical drapes. Recipients whose native kidneys produce urine will naturally fill up the urinary bladder; those individuals whose kidneys do not will require insufflation of saline prior to creation of the ureteral anastomosis.

Exposure of the operative field starts with a curvilinear skin incision, one to two finger widths above the midline pubic bone and the lateral edge of the rectus sheath. Superiorly, the extension of the incision depends on the recipient's body habitus and the size of the donor kidney. The anterior rectus sheath is incised, medially to laterally, until the lateral edge of the rectus sheath is exposed. The posterior rectus sheath is missing below the arcuate line, thus providing direct access to the extraperitoneal space. The rectus muscle can be easily mobilized medially without being divided. The remainder of the fascial incision is along the lateral edge of the rectus sheath until the desired exposure is achieved (Fig. 11-6).

The retroperitoneal space of the iliac fossa is entered by mobilizing the peritoneum medially. The inferior epigastric vessels, the round ligament (in females), and the spermatic cord and its vasculature (in males) are encountered in this space; the former two structures are divided, while the latter is retracted with a vascular loop. A self-retained retractor is used to expose the surgical field. The iliac vessels should be dissected with great care. To minimize the risk of lymphocele development postoperatively, dissection of the iliac artery should be limited; the intertwining lymphatics around the iliac vessels should be ligated. In general, the donor's renal artery and vein are anastomosed to the recipient's external iliac vessels in an end-to-side fashion (Fig. 11-7). In recipients with a severely calcified iliac artery, the internal iliac artery can be used as an alternative, and in select cases, an endarterectomy must be performed.

After restoring the circulation to the donor's kidney, urinary continuity can be established via several approaches. The approach chosen depends on such factors as the length of the donor ureter and a recipient history of bladder surgery, native

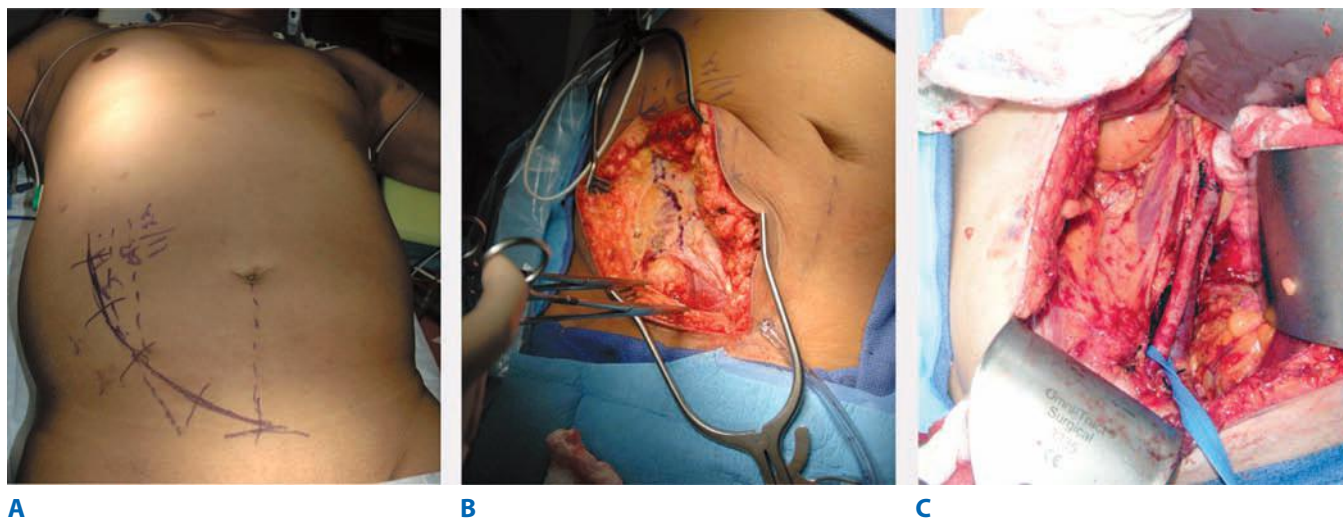


Figure 11-6. Incision and exposure for kidney transplant. **A.** Mark for the skin incision. **B.** Anterior rectus sheath incised obliquely. The abdominal muscle transected lateral to the rectus muscle. **C.** External iliac artery and vein dissected.

nephrectomy, or pelvic radiation. The two most common procedures to restore urinary continuity are the Leadbetter-Politano and a modification of the Lich (e.g., extravesical) ureteroneocystostomy, which actually was designed to avoid ureteral reimplantation.

During the former procedure, a large cystostomy is created in the dome of the bladder, and the donor ureter is brought through a lateral and somewhat inferior 1-cm submucosal tunnel into the bladder, the end of which is spatulated and then sewn in place without tension with interrupted absorbable sutures placed through the mucosa and submucosa on the inside of the bladder.

An extravesical ureteroneocystostomy is performed by careful dissection of a 1-cm portion of the muscular layers on the anterolateral portion of the bladder until a “bubble” of mucosa is exposed. The donor ureter is spatulated in a diamond-shaped fashion, the bladder mucosa is incised, absorbable interrupted sutures are placed in four quadrants, and a mucosa-to-mucosa anastomosis is created using running absorbable sutures with a temporary ureteral stent in place of the first three-quarters of

the anastomosis. The muscular layers of the bladder are then carefully approximated over the anastomosis to prevent reflux.

The decision to place a ureteral stent depends on the surgeon, who must try to balance the risk of infectious complications with the possible technical complications of a ureteral anastomosis, but in general, this is not required except during the rarely performed donor ureter to recipient ureter anastomosis or in the case of a pediatric kidney transplant. Fixation of the donor’s kidneys is not necessary, except in the case of small kidneys (usually from a pediatric donor) or en bloc kidneys.

Grafts with Multiple Renal Arteries

In 10% to 30% of donor kidneys, multiple renal arteries are encountered. Unless kidney transplant candidates have hypercoagulopathy, grafts with multiple renal arteries fare as well as those with single vessels.⁸⁶ Vascular reconstruction options include implanting the donor’s arteries separately, reconstructing the multiple arteries into a common channel, or combining multiple arteries into a common Carrel patch (Fig. 11-8).

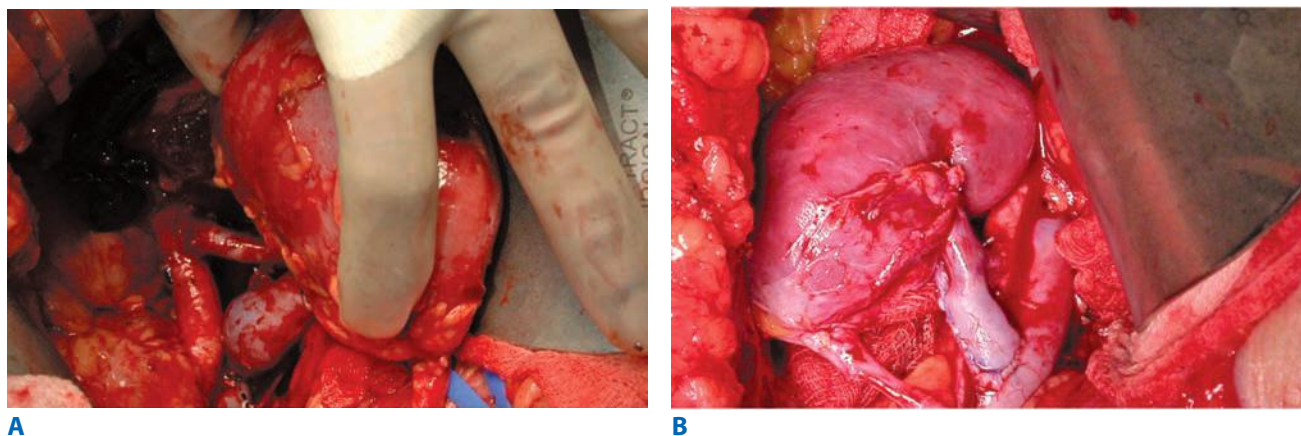


Figure 11-7. Vascular anastomoses of kidney transplant. **A.** Arterial anastomosis: donor renal artery with Carrel patch to recipient external iliac artery, end-to-side. **B.** Venous anastomosis: donor renal vein with caval extension conduit to recipient external iliac vein, end-to-side.

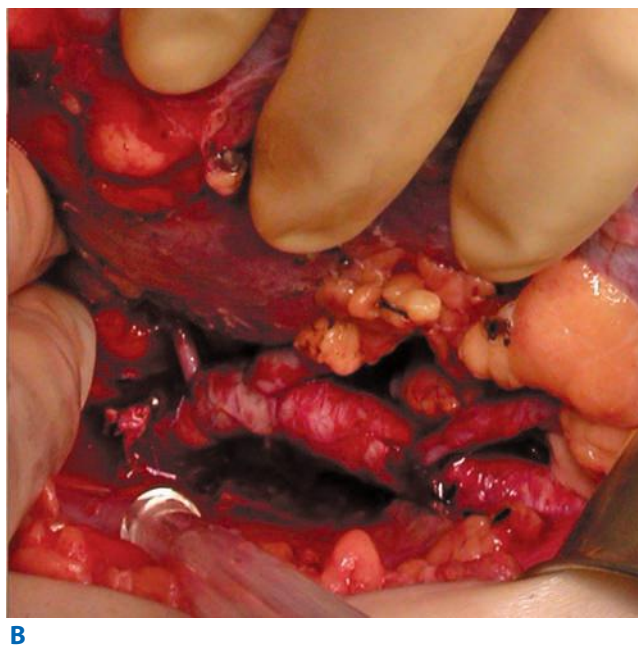
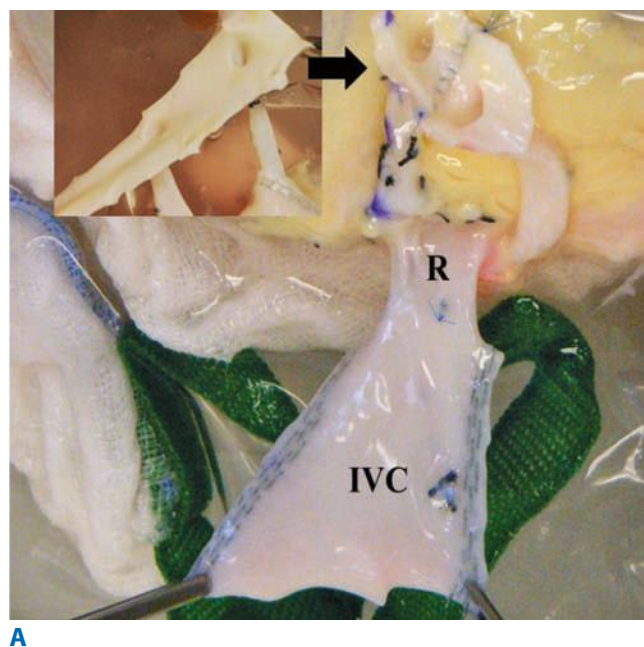


Figure 11-8. Arterial and venous reconstruction. **A.** Two renal arteries combined into a single Carrel patch (arrow). Right renal vein extension conduit constructed with stapled caval patch. IVC = inferior vena cava; R = right renal vein. **B.** Three renal arteries anastomosed to external iliac artery separately.

En Bloc Grafts

Debate persists about whether to implant kidneys obtained from young donors (<5 years or whose body weight is under 20 kg) as a single en bloc unit into one recipient or separately into two recipients. The underlying issues are the shortage of donor organs, the complexity of the surgical procedure, the risks of graft thrombosis, ureteral complications, and long-term outcomes.

In en bloc kidney transplants, the donor aorta and vena cava are used as the vascular inflow and outflow conduits. Therefore, reconstruction of the en bloc graft pretransplant is key to a successful transplant. The donor's suprarenal vena cava and aorta are oversewn. The lumbar branches of the cava and aorta are ligated. Dissection around the renal hilum should be avoided. The orientation of the cava and aorta should be

clearly marked, in order to avoid torsion of the anastomosis. If the color of the two kidneys looks different after reperfusion, repositioning should be attempted to rule out vascular torsion; fixation of the en bloc kidneys to the retroperitoneum is often necessary. The donor's ureters are implanted to the recipient's bladder, either as two separate anastomoses or as a common patch (Fig. 11-9). Only a handful of centers have performed en bloc kidney transplants, but the long-term outcomes are encouraging.^{87,88}

Perioperative Care

Preoperatively, a thorough history and physical examination should be performed. Any changes in transplant candidates' recent medical history should be investigated in great detail.

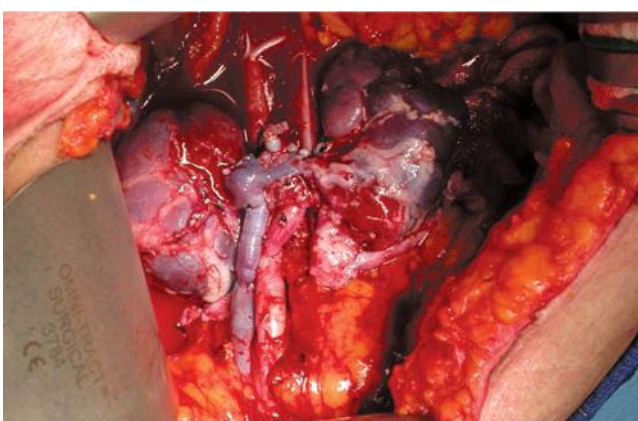


Figure 11-9. En bloc kidney transplant (3-month-old donor kidneys). **A.** En bloc kidneys benched. Vascular integrity tested with methylene blue (blue hue look of the kidneys). **B.** En bloc kidneys transplanted in to a 62-year-old woman. Donor aorta anastomosed to recipient's external iliac artery; donor cava, to recipient's external iliac vein.

In those recipients with a historically negative PRA level who have recently undergone blood transfusions, a prospective tissue cross-match is necessary to avoid graft rejection. Electrolyte panels should be checked. Emergency dialysis may be necessary for transplant candidates experiencing hyperkalemia or fluid overload.

For dialysis-dependent transplant candidates, the catheter sites should be examined preoperatively to rule out infections. Vascular access for hemodialysis is essential to avoid complications related to posttransplant acute tubular necrosis (ATN). Vascular evaluation is mandatory; any changes in results should be investigated by appropriate imaging studies.

As is routine for other major surgical procedures, transplant candidates should preoperatively undergo a chest x-ray, a 12-lead ECG, blood typing, cross-match tests, and prophylaxis against surgical site infection (by administration of a nonnephrotoxic antibiotic with activity against both common skin microflora and gram-negative pathogens); candidates should receive nothing to eat or drink.

Intraoperatively, transplant recipients should be kept well-hydrated to avoid ATN and should receive heparin prior to vascular occlusion. Before reperfusion of the transplanted kidney, the desired central venous pressure should be maintained at around 10 mmHg, and the systolic blood pressure should be above 120 mmHg. In pediatric recipients of an adult graft, a superphysiologic condition may be necessary to avoid ATN or graft thrombosis. Mannitol often is administered before reperfusion as a radical scavenger and diuretic agent, and a diuretic such as furosemide is administered as well.

Postoperatively, the guiding principles for the care of kidney transplant recipients are the same as for other surgical patients. The crucial elements include hemodynamic stability and fluid and electrolyte balance. To achieve a euvolemic state, the recipient's urine output is replaced with either an equal or a reduced volume of IV fluid on an hourly basis, depending on the medical status. In recipients undergoing brisk diuresis, aggressive replacement of electrolytes (including calcium, magnesium, and potassium) may be necessary. In recipients experiencing ATN, fluid overload, or hyperkalemia, however, fluid restriction, treatment for hyperkalemia, and even hemodialysis may be necessary.

Hypotension is an unusual event immediately posttransplant. The differential diagnoses include hypovolemia, vasodilation, and myocardial infarction with cardiac failure. Immediate action should be taken to avoid life-threatening complications. Posttransplant hypertension can be mediated by catecholamines, fluid overload, or immunosuppressive agents.

Postoperatively, urine output is used as a surrogate marker to monitor graft function. Among recipients whose native kidneys produce significant amounts of urine, normal or increased urine output can be misleading; for them, serum blood urea nitrogen and creatinine levels are more reliable indicators of kidney graft function.

Suddenly decreased or minimal urine output requires immediate attention. A change in volume status is the most common cause, but other culprits include blockage of the urinary catheter, urinary leak, vascular thrombosis, hypotension, drug-related nephrotoxicity, ATN, and rejection (all of which must be thoroughly investigated). Diagnostic studies such as Doppler ultrasound, nuclear renograms, or biopsies should be considered.

Postoperative bleeding is an uncommon event after a kidney transplant. Recipients on anticoagulation or antiplatelet

treatments are at increased risk. Signs and symptoms (such as an expanding hematoma over the surgical site, increased pain over the graft, a falling hemoglobin level, hypotension, and tachycardia) should arouse suspicion of hemorrhage. Doppler ultrasound is useful to establish the underlying cause. Surgical exploration seldom is required, because the accumulated hematoma tamponades the bleed. Indications for surgical exploration include ongoing transfusion requirement, hemodynamic instability, and graft dysfunction from hematoma compression. For recipients on anticoagulation or antiplatelet treatments, the threshold for surgical exploration is lower. Small unligated vessels at the donor's renal hilum or recipient's retroperitoneum are likely sources of bleeding.

One of the most devastating postoperative complications in kidney recipients is graft thrombosis. It is rare, occurring in fewer than 1% of recipients. The recipient risk factors include a history of recipient hypercoagulopathy and severe peripheral vascular disease; donor-related risk factors include the use of en bloc or pediatric donor kidneys, procurement damage, technical factors such as intimal dissection or torsion of vessels, and hyperacute rejection. Graft thrombosis usually occurs within the first several days posttransplant. Acute cessation of urine output in recipients with brittle posttransplant diuresis and the sudden onset of hematuria or graft pain should arouse suspicion of graft thrombosis. Doppler ultrasound may help confirm the diagnosis. In cases of graft thrombosis, an urgent thrombectomy is indicated; however, it rarely results in graft salvage.

Urologic complications are seen in up to 5% of recipients. The cause is often related to ureteral ischemia, damage during procurement of the donor's distal ureter, or technical errors. Symptoms of urine leak include fever, pain, swelling at the graft site, increased creatinine level, decreased urine output, and cutaneous urinary drainage. Diagnosis can be confirmed by a combination of ultrasound, nuclear renography, drainage of perinephric fluid collection, and comparison of serum and fluid creatinine levels. Depending on the location and volume of the urine leak, satisfactory results can be achieved by surgical exploration and repair or by percutaneous placement of a nephrostomy and ureteral stenting.

Early urinary obstruction can be due to edema, blood clots, torsion of the ureter, or compression from a hematoma. Late urinary obstruction is often related to ischemia. The appearance of hydronephrosis on ultrasound is a good initial indicator. Treatment includes percutaneous placement of a nephrostomy and ureteral stenting. If transluminal intervention fails, surgical intervention (such as ureteral reimplantation or a ureteropyelostomy) can be undertaken.

Results

A kidney transplant remains the most common solid organ transplant in the world today. With the introduction of induction immunosuppressive therapy and ever-improving, less toxic immunosuppressive medications, posttransplant outcomes have become better and better. According to a recent analysis of more than 250,000 U.S. adult kidney transplant recipients, the actual half-life (50% graft survival) of a deceased donor kidney was 6.6 years in 1989, 8 years in 1995, and 8.8 years in 2005. Interestingly, during that same period—though with a much better overall outcome—the half-life of a living donor kidney has essentially remained the same: 11.4 years in 1989 and 11.9 years in 2005.⁸⁹

The biggest improvements have been in the reduction of 1-year graft failure. With a deceased donor kidney, the 1-year graft failure rate dropped from 20% in 1989 to less than 7% in 2009; with a living donor kidney, the rate dropped from 8.5% in 1989 to less than 3% in 2009.⁸⁹ Furthermore, steroid-free protocols⁹⁰ and calcineurin-free protocols⁹¹ have been validated and implemented in the last two decades, further reducing medication-related side effects and vastly improving the quality of life for tens of thousands of recipients.

Currently, the most common cause of graft loss is recipient death (usually from cardiovascular causes) with a functioning graft. The second most common cause is chronic allograft nephropathy; characterized by a slow, unrelenting deterioration of graft function, it likely has multiple causes (both immunologic and nonimmunologic).^{92,93} The graft failure rate due to complications related to surgical technique has remained at about 2%.

PANCREAS TRANSPLANTATION

A successful pancreas transplant is currently the only definitive long-term treatment for patients with insulin-dependent diabetes mellitus (IDDM) that (a) restores normal glucose hemostasis without exposing patients to the risk of severe hypoglycemia and (b) prevents, halts, or reverses the development or progression of secondary complications of diabetes.⁹⁴

Given its vast medical, social, and financial implications, diabetes mellitus is a huge burden to patients and to society as a whole. An estimated 10% to 15% of the U.S. population is affected by it; of all diabetic patients, 10% have early-onset disease. In the United States, diabetes mellitus is the most common cause of end-stage kidney disease, blindness, impotence, major limb amputations, and coronary or peripheral vascular bypass procedures. It is one of the most common causes of death, along with myocardial infarction and stroke. Diabetes significantly decreases not only the quality of life but also life expectancy.

Despite improvements in exogenous insulin administration (including the use of devices such as insulin pumps), wide fluctuations in glucose levels and the risk of hypoglycemic episodes are common. The Diabetes Control and Complications Trial (DCCT) demonstrated in the late 1990s that intensive insulin therapy may slow the rate of secondary complications of diabetes—yet at the expense of (life-threatening) iatrogenic hypoglycemia. The annual mortality rate of patients with insulin-induced inadvertent hypoglycemia is estimated to be as high as 2% to 3%.

Since the first pancreas transplant in December 1966, performed by William Kelly and Richard Lillehei at the University of Minnesota, more than 25,000 pancreas transplants in the United States and more than 10,000 pancreas transplants from all over the world have been reported to the International Pancreas Transplant Registry (IPTR), which is maintained at the University of Arizona.^{94,95}

Pancreas transplants are performed in three recipient categories:

- *Simultaneous pancreas and kidney (SPK) transplant in diabetic and uremic patients.* Almost 80% of pancreas transplants are performed in this category. The recipient is already obligated to lifelong immunosuppressive therapy, due to the need for a kidney transplant, so only the surgical risk of a pancreas transplant is added. A successful SPK

transplant renders the recipient dialysis-free and insulin-independent.

- *Pancreas after kidney (PAK) transplant in diabetic and posturemic patients.* Approximately 15% of all pancreas transplants fall into this category. These patients previously underwent a kidney transplant with either a living or deceased donor, but are candidates for a subsequent pancreas transplant because of poor glucose control or because of progression of secondary diabetic complications (which may include the development of diabetic nephropathy in the transplanted kidney).
- *Pancreas transplant alone (PTA) in nonuremic patients with brittle diabetes mellitus.* Only about 8% of all pancreas transplants are in this category. These patients have not yet developed advanced diabetic nephropathy, but their glucose levels are extremely labile despite best efforts to control it. Because of the lifelong need for immunosuppressive therapy, the surgical risk has to be balanced with the medical risks of brittle diabetes (e.g., frequent episodes of hypoglycemia and hypoglycemic unawareness).

In SPK recipients, a plethora of literature exists that demonstrates significant improvements in secondary diabetic complications (across all organ systems) posttransplant. Improvements have been reported in diabetic nephropathy, neuropathy (autonomic and peripheral), micro- and macrovascular disease, retinopathy, gastroparesis, and other secondary complications.⁹⁶ Currently, more than 1000 pancreas transplants are performed annually in the United States, with the goal of conferring the following benefits: excellent glucose control (similar to that of a functioning native pancreas), prevention or improvement of secondary diabetic complications, and increased quality of life and life expectancy. In addition, pancreas transplants can be successfully performed in patients who have undergone a total pancreatectomy for benign disease (such as chronic pancreatitis) to treat both endocrine and exocrine deficiency after surgery.⁹⁷

Donor Operation

The general criteria for selecting deceased donors for pancreas procurement are similar to those for other solid organs; a history of type 1 diabetes mellitus obviously is a contraindication. Relative contraindications include previous pancreatic procedure(s), as well as pancreatic disorders, such as chronic pancreatitis and intraductal papillary mucinous neoplasm. Hyperglycemia in itself is not a contraindication to pancreas procurement, because its cause in brain-dead donors usually is severe insulin resistance, which is rarely observed in recipients.

In light of better anatomic understanding and improved surgical skills, all three abdominal organs that share a common blood supply (pancreas, liver, and intestine) can be procured at the same time and transplanted into three different recipients (Fig. 11-10). During pancreas procurement, a “no-touch” technique of the gland is preferred; dissection of the pancreas is carried out in a way that avoids direct manipulation of the organ such that simultaneous procurement of the spleen, duodenum, and surrounding connective tissues occurs.

In contrast to the liver and kidneys, the pancreas should not be extensively flushed at the end of the procurement. To minimize the amount of preservation fluid that reaches the pancreas, the splenic artery and SMA can be temporarily clamped at their origin from the aorta. Usually, the celiac axis with an

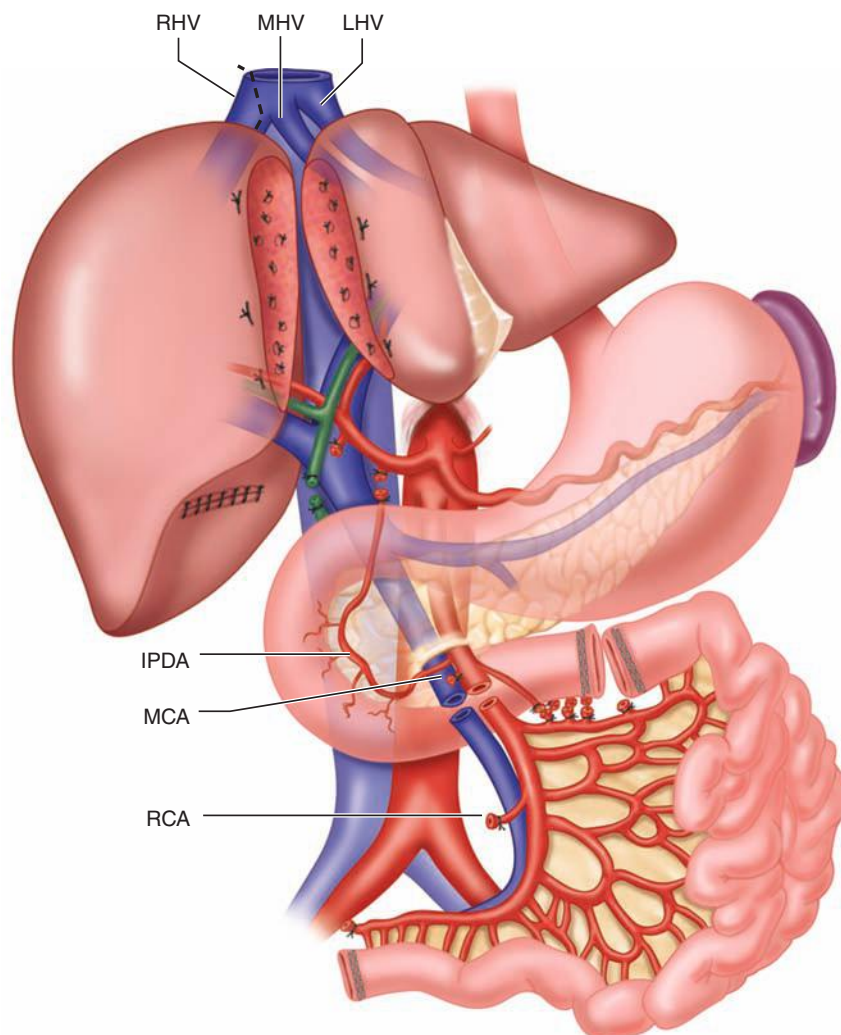


Figure 11-10. Simultaneous pancreas, in situ split-liver, and intestine procurement. IPDA = inferior pancreaticoduodenal artery; LHV = left hepatic vein; MCA = middle cerebral artery; MHV = middle hepatic vein; RCA = right coronary artery; RHV = right hepatic vein. (Reproduced from Gruessner RWG, Sutherland DER, eds. *Transplantation of the Pancreas*. New York: Springer, 2004; Color Plate VI, Figure 8.1.3.11. With kind permission of Springer Science + Business Media.)

aortic Carrel patch is retained with the liver. The splenic artery is divided close to its origin and is retained with the pancreas. The SMA is also procured with an aortic Carrel patch and is retained with the pancreas.

In case of a replaced or aberrant right hepatic artery, this first branch off of the SMA is carefully dissected out from the posterior surface of the pancreas. A replaced or aberrant right hepatic artery does not transverse the pancreas and is not a contraindication to combined pancreas and liver procurement. But with this anatomic variant, an aortic Carrel patch with the proximal SMA and replaced or aberrant right hepatic artery remains with the liver; the distal SMA with the inferior pancreaticoduodenal artery remains with the pancreas.

In the relatively rare event that the liver is not procured, then neither the splenic nor the gastroduodenal arteries need to be divided at their respective takeoff; the donor's celiac axis and the SMA are included on a common Carrel patch. This technique allows a single arterial anastomosis to be performed in the recipient without reconstruction. At the end of the procurement, the pancreas is attached to the spleen, duodenum, and proximal jejunum, which is stapled at both ends.⁹⁸

Back Table Preparation of the Pancreas Graft

Back table preparation of the pancreas graft consists of four steps: (a) removal of the spleen; (b) shortening, restapling, and/

or suture reinforcement of the mesenteric root; (c) trimming of any excess distal and proximal duodenum, along with reinforcement of the proximal staple line; and (d) arterial reconstruction.

Back table preparation is carried out in a basin filled with chilled preservation solution. The most common technique to create a single arterial inflow to the pancreas graft is the "Y-graft" reconstruction, using a resected segment of the donor iliac artery bifurcation. In this technique, the donor external iliac artery is anastomosed end-to-end to the donor SMA, and the donor internal iliac artery is anastomosed end-to-end to the splenic artery (Fig. 11-11). This procedure allows the donor common iliac artery to be anastomosed as a single vessel to the recipient's common iliac artery. For venous outflow, the portal vein is kept relatively short, in order to avoid the risk of venous thrombosis by kinking or impingement.⁹⁸

Recipient Operation

Over the years, different surgical techniques have been described for (a) the management of exocrine pancreatic secretions and (b) the type of venous drainage. For the secretions, the two most common techniques are drainage of the duodenal segment to the bladder (bladder drainage) or to the small bowel (enteric drainage) (Figs. 11-12 and 11-13). For venous drainage, systemic venous drainage is preferred over portal venous drainage.

The pancreas graft is usually placed intra-abdominally and preferably on the right side, because the iliac vessels are in a more

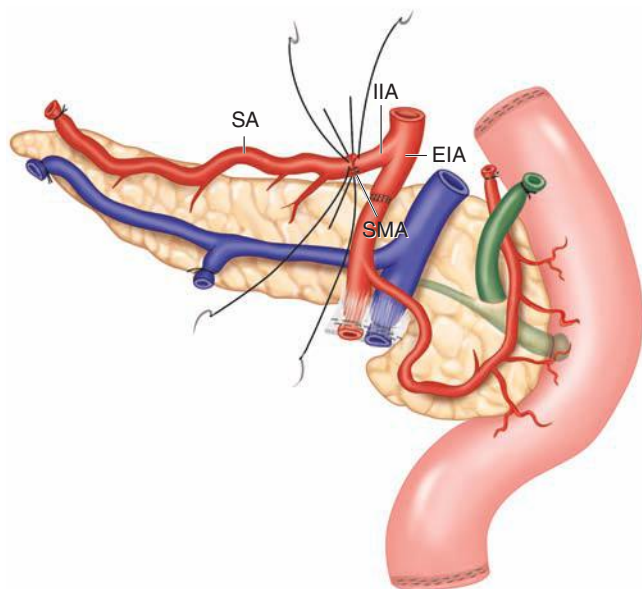


Figure 11-11. Posterior view of the pancreas graft with Y-graft reconstruction. EIA = external iliac artery; IIA = internal iliac artery; SA = splenic artery; SMA = superior mesenteric artery. (Reproduced from Gruessner RWG, Sutherland DER, eds. *Transplantation of the Pancreas*. New York: Springer, 2004; Color Plate VII, Figure 8.1.3.13[B]. With kind permission of Springer Science + Business Media.)

shallow position on the right than on the left side; moreover, the vessels are already appropriately aligned for the vascular anastomoses (i.e., a lateral position for the common iliac vein, a medial position for the common iliac artery). Venous and arterial anastomoses are performed end-to-side. After restoration of

blood flow to the graft, hemostasis must be meticulously maintained. Because the donor portal vein purposely is kept short, ligation and transection of all of the recipient's internal iliac vein branches are frequently performed, in order to prevent tension on the venous anastomosis. The pancreas usually is placed with the pancreatic head and duodenum pointing caudally.

Bladder drainage is performed using either a hand-sewn or a stapled anastomosis in which the antimesenteric side of the donor duodenum is sewn to the superior portion of the dome of the bladder. The stapled technique requires that a circular cutting stapler be inserted through the open distal end of the donor duodenum, which is subsequently closed. Bladder drainage has two main advantages. First, rejection of the exocrine pancreas precedes rejection of the endocrine pancreas by 5 to 7 days. Amylase levels are measured routinely in the recipient's urine. With bladder drainage, antirejection treatment can successfully be implemented when the recipient is still normoglycemic and only hypoamylasuric. In the absence of hyperglycemia, more than 90% of pancreas rejection episodes are reversible. Second, bladder drainage avoids the bacterial contamination that occurs with enteric drainage. If an anastomotic leak occurs, it is easier to treat, because the infection usually remains localized to the right lower quadrant.

Enteric drainage is more physiologic and has advantages as well. The antimesenteric side of the donor's duodenum is anastomosed to the antimesenteric portion of the recipient's jejunum in a side-to-side fashion. The enteric anastomosis can also involve a defunctionalized Roux-en-Y loop, which minimizes the potential complications if an enteric leak occurs.⁹⁸ Currently, in the United States, more than 80% of all pancreas transplants are performed with enteric drainage for the exocrine pancreatic secretions, and more than 90% employ systemic venous drainage.⁹⁵

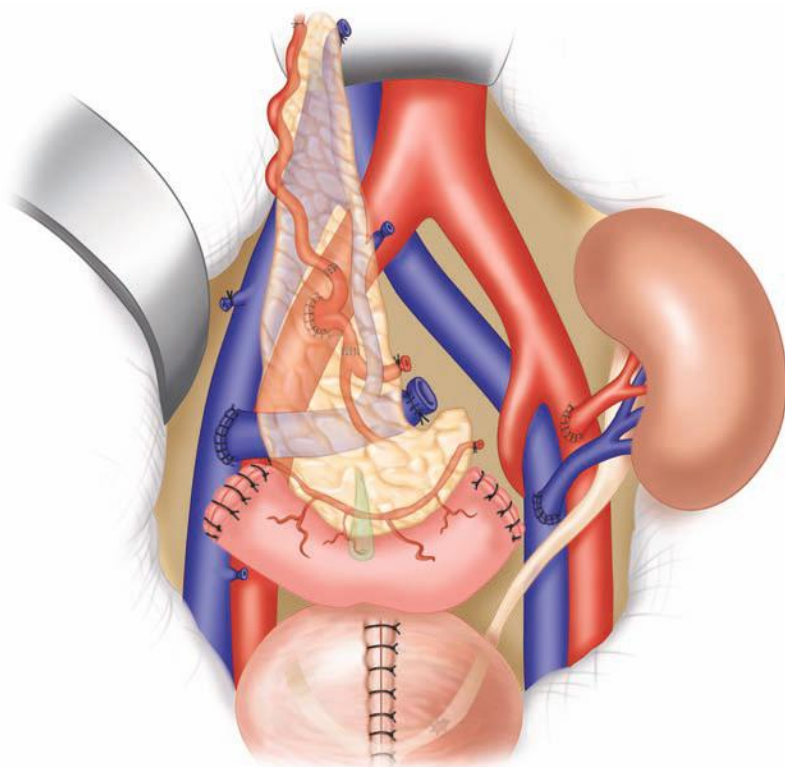


Figure 11-12. Whole-organ transplant with systemic vein and bladder exocrine drainage. (Reproduced from Gruessner RWG, Sutherland DER, eds. *Transplantation of the Pancreas*. New York: Springer, 2004; Color Plate XIV, Figure 8.2.2.2[B]. With kind permission of Springer Science + Business Media.)

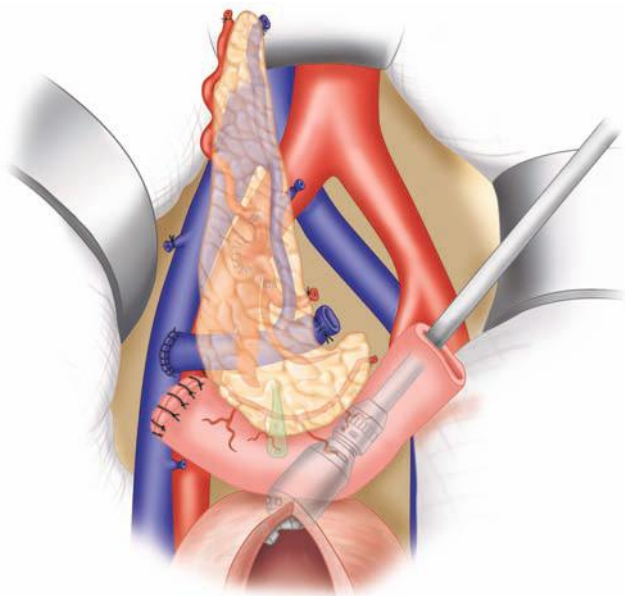


Figure 11-13. Whole-organ transplant with systemic vein and enteric exocrine drainage. (Reproduced from Gruessner RWG, Sutherland DER, eds. *Transplantation of the Pancreas*. New York: Springer, 2004; Color Plate XIV, Figure 8.2.2.2[A]. With kind permission of Springer Science + Business Media.)

Complications

The technical complication rate for pancreas transplants is higher than for any other solid organ transplant. Four factors contribute to the high surgical complication rate⁹⁹: (a) the nature of the organ itself with inherent organ-specific surgical complications (e.g., pancreatitis, abscesses, necrosis, fistulas, and pseudocysts) and its low blood flow (which significantly increases the risk of thrombosis, as compared with a kidney or liver transplant); (b) the risk of a leak or infection after connecting two hollow viscera (the duodenum and either the bladder or small intestine); (c) the increased incidence of rejection episodes, because the pancreas is one of the most immunogenic solid organs; and (d) the underlying disease of diabetes mellitus, predisposing patients not only to infections but also to cardiovascular and other complications.

The most common surgical complications are thrombosis (an incidence of 5%–15%), intra-abdominal abscesses (5%–10%), and bleeding (6%–8%). Other pancreas-specific complications include graft pancreatitis (frequently due to procurement or reperfusion injury), pancreatic fistulas, and pancreatic pseudocysts. Anastomotic leaks do not always require a graft pancreatectomy, but arterial pseudoaneurysms, arteriovenous fistulas, and wound dehiscence may. Bleeding frequently requires relaparotomy.

Thrombosis usually occurs within the first week posttransplant. It manifests as a sudden increase in insulin requirements or as a sharp drop in urinary amylase levels. Venous thrombosis, which is more common than arterial thrombosis, is associated with distinct clinical symptoms, including a swollen and tender graft, hematuria, lower extremity edema, and deep vein thrombosis, the latter two occurring ipsilaterally. Arterial thrombosis is less symptomatic and may not initially cause pain; its diagnosis is usually confirmed by Doppler ultrasonography. Surgical exploration in recipients with thrombosis usually requires a graft pancreatectomy.

With the advent of advanced interventional radiologic procedures to drain intra-abdominal abscesses, the reoperation rate has markedly decreased. Pancreas transplant recipients are usually kept on broad-spectrum antimicrobial agents for the first 7 days posttransplant.

The most common nonsurgical complication posttransplant is rejection. The incidence of rejection is about 30% within the first year. The diagnosis is usually based on an increase in serum amylase and lipase levels and, in bladder-drained recipients, a decrease in urinary amylase levels. A sustained drop in urinary amylase levels greater than 25% from baseline should prompt a pancreas graft biopsy to rule out rejection. In enteric-drained recipients, one must rely on serum amylase and lipase levels only. Other signs and symptoms of rejection include tenderness over the graft, unexplained fever, and hyperglycemia, which usually is a late finding; fewer than 5% of all rejection episodes can be reversed in its presence. The diagnosis of rejection should be confirmed by a percutaneous pancreas graft biopsy.

Other nonsurgical complications include infections with CMV, HCV, or extra-abdominal bacteria or fungi; malignancies, such as PTLN; and, rarely, graft-versus-host disease. For such complications, the diagnosis and treatment are similar to what is recommended after other solid organ transplants.

Bladder-drained pancreas recipients may experience an array of unique urologic complications. Usually the result of the irritating nature of pancreatic enzymes on the urothelium in the bladder and urethra, these urologic complications can lead to cystitis, hematuria, and dysuria. With the loss of bicarbonate from pancreatic secretions, dehydration and metabolic acidosis are not uncommon. Many of these complications are chronic, such that approximately 20% to 30% of all bladder-drained recipients require conversion to enteric drainage within the first 5 years posttransplant.¹⁰⁰

Living Donor Pancreas Transplants

Pancreas transplants using living donors also can be performed safely and successfully in select donors and recipients. Since 1979, about 150 such transplants have been performed worldwide, with 1-year graft survival rates in excess of 85% over the last decade. A meticulous donor evaluation using standard criteria remains key to a low donor metabolic and surgical complication rate. The concept of procuring the distal pancreas from a living donor is based on the observation that patients with benign or malignant pancreatic disorders can undergo a distal hemipancreatectomy without any serious change in endocrine function.

Living donor pancreas transplants are ideal for patients with an identical twin, but other relatives can be suitable donors as well. In particular, patients with high PRA levels should be considered for a living donor transplant.

Living donor pancreas transplants decrease the number of deaths of diabetic patients on the waiting list, help overcome the organ shortage, reduce mortality and morbidity, and improve the quality of life for patients with debilitating side effects of diabetes. The use of living donors also reduces the risk of graft rejection, as compared with the use of deceased donors. Yet living donor pancreas transplants remain relatively rare, performed under very selective circumstances. In terms of surgical technique, the donor splenic artery and vein are anastomosed to the recipient's external iliac artery and vein in an end-to-side fashion, and exocrine drainage can occur via an anastomosis

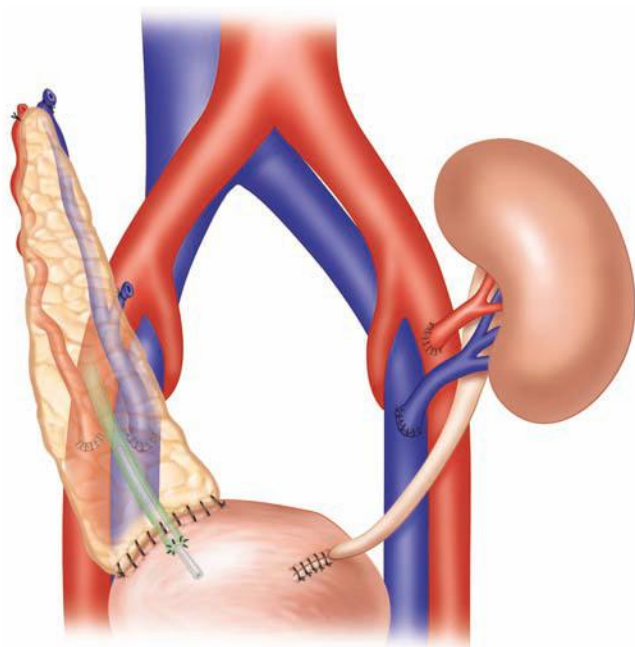


Figure 11-14. Segmental transplant with systemic vein and bladder exocrine drainage. The donor splenic artery and splenic vein are anastomosed end-to-side to the recipient's external iliac artery and vein. The splenic artery anastomosis is lateral and proximal to the splenic vein anastomosis. A two-layer ductocystostomy is constructed. (Reproduced from Gruessner RWG, Sutherland DER, eds. *Transplantation of the Pancreas*. New York: Springer, 2004; Color Plate XVI, Figure 8.2.2.4. With kind permission of Springer Science + Business Media.)

of the pancreatic duct and transected end of the pancreas to the bladder or bowel¹⁰¹ (Fig. 11-14).

Results

As of December 2010, more than 35,000 pancreas transplants had been reported to the IPTR: more than 25,000 transplants in the United States and more than 10,000 in other countries. According to IPTR data, recipient age at the time of the transplant has increased significantly, and so has the number of transplants for patients with type 2 diabetes. The trend over time has been toward stricter donor criteria, with a concentration on younger donors, preferably trauma victims, and on short pancreas graft preservation time.

Drainage techniques have changed over time, too: enteric drainage of exocrine pancreatic secretions is now predominant, in combination with systemic drainage of the venous effluent of the pancreas graft. Immunosuppressive protocols have developed toward antibody induction therapy, followed by administration of tacrolimus and MMF for maintenance. Steroid avoidance has increased over time in all three recipient categories.

These changes have led to improved patient and graft survival rates. In all three recipient categories, early technical graft loss rates have decreased significantly to about 8%. Likewise, the 1-year immunologic graft loss rate has also decreased, ranging from 2% to 6%. The 1-year patient survival rates now exceed 90% in all three recipient categories. The highest 1-year pancreas graft survival rate is in SPK recipients: 86% for the pancreas and 93% for the kidney. The 1-year pancreas graft survival rate is 80% in PAK recipients and 78% in PTA recipients.

Significant improvements have been noted not only in 1-year pancreas graft function but also in long-term success rates. The most recent 5-, 10-, and 20-year pancreas graft function rates are 80%, 68%, and 45% for SPK recipients; 62%, 46%, and 16% for PAK recipients; and 59%, 39%, and 12% for PTA recipients, respectively. The quality of the deceased donor graft is of paramount importance. The use of anti-T-cell induction therapy has had a significant impact on long-term graft survival, specifically in PTA recipients.

IPTR data show significant improvements in patient survival and pancreas graft function rates since the inception of UNOS, over a course of 24 years.^{92,95,99,102} Clearly, pancreas transplants now offer excellent outcomes for patients with IDDM.

Islet vs. Pancreas Transplants

Pancreas transplants are frequently compared with islet transplants, which are less invasive and, therefore, more appealing. It is important to emphasize that these two types of transplants are not mutually exclusive but rather complementary. The results of islet transplants have improved over the past decade, but overall islet graft function, specifically long-term function, still significantly trails overall pancreas graft function.¹⁰³

6▶ Islet transplants involve pancreas procurement (as described earlier) and then separation of islets from the exocrine pancreatic tissues using proteolytic enzymes (as described later). The human pancreas contains about one million islets, of which half are lost during the isolation process. About 10,000 islets per kilogram of body weight are needed to achieve insulin independence when transplanted into the liver. Frequently, one donor pancreas does not suffice; in fact, up to four donor pancreases have been used for one islet recipient.

Because of the relatively disappointing long-term outcomes, insurance providers in the United States do not provide reimbursement for islet transplants. Transplant centers with both pancreas and islet transplant programs follow an algorithm that favors islet transplants in patients with a high surgical risk and pancreas transplants in patients with a low surgical risk. Although solitary donor pancreases are not in short supply, only one donor pancreas is required for a successful pancreas transplant; in contrast, two to four donor pancreases are commonly used for one islet recipient with less favorable long-term outcomes.

Of note, the primary goal of current islet transplant trials is not insulin independence but rather a reduction in the incidence and severity of hypoglycemic events, a reduction in exogenous insulin requirements, and an amelioration of hemoglobin A_{1c} levels. Islet transplants rarely maintain long-term insulin independence. A recent study showed a higher rate of insulin independence in PTA recipients than in recipients of an islet transplant alone, despite the use of up to three donor pancreases in each of the islet recipients.¹⁰⁴ Until islet transplant results significantly improve and include long-term insulin independence, a pancreas transplant remains the treatment of choice for β -cell replacement therapy in patients with IDDM.

ISLET TRANSPLANTATION

Transplanting islets of Langerhans isolated from deceased donor pancreases is an appealing option for patients with type 1 diabetes. An islet transplant involves the procurement of a donor pancreas and its transportation to a specialized islet

isolation facility, where the pancreas is enzymatically digested; then, the islets are purified from the rest of the digested pancreas using density gradients. The purified islets are then cultured and evaluated for their identity, viability, and potency, before being infused into the portal vein of a diabetic recipient. When the procedure is successful, these islet cells engraft into the recipient and secrete insulin, providing excellent moment-to-moment control of blood glucose, as is seen with a whole-pancreas transplant.

A successful islet transplant offers advantages over exogenous insulin injections—advantages that are similar to those of a whole-pancreas transplant. These advantages include restoring β -cell secretory capacity, improving glucose counterregulation, restoring hypoglycemia awareness, providing perfect or near-perfect glucose homeostasis, and, potentially, preventing secondary diabetic complications.

Unlike a whole-pancreas transplant, an islet transplant does not involve a major surgical procedure with its associated mortality and morbidity. Instead, it can generally be performed as an outpatient procedure using percutaneous catheter-based therapy to cannulate a branch of the portal vein, with minimal recovery time for the recipient. Potential complications associated with islet injection include portal hypertension, portal vein thrombosis, hepatic abscesses, and bacteremia. Theoretically, islet transplants could have wider application (as compared with current practice and with whole-pancreas transplants), given the significantly lower surgical risk, the relatively small tissue volume transplanted, and the potential for islet immunomodulation or immunoisolation, which could minimize or eliminate the need for immunosuppression.

The first reported attempt at an islet transplant was in 1893 by Watson-Williams and Harsant: they transplanted a sheep's minced pancreas into the subcutaneous tissue of a young boy with ketoacidosis.¹⁰⁵ The discovery of insulin may have reduced interest in islet transplants as a treatment for diabetes, at least until the realization that insulin could not provide perfect glyce-mic control and that, therefore, patients ultimately suffered devastating secondary complications. Several milestones ensued: the first whole-pancreas transplants,¹⁰⁶ early success with rodent islet transplants,¹⁰⁷ and then, in the 1970s, human islet autotransplants after pancreatectomy, in order to address the intractable pain associated with chronic pancreatitis, by Sutherland, Najarian, and colleagues in Minnesota.¹⁰⁸

Until recently, attempts to extend those trailblazing findings of clinical islet autotransplants to clinical islet allotransplants in patients with type 1 diabetes met with generally very poor success. For example, in 1995, a report of the International Islet Transplant Registry indicated that of 270 recipients, only 5% were insulin-independent at 1 year posttransplant.

In 2000, Shapiro and colleagues reported the results of the Edmonton protocol, which enabled consistent diabetes reversal and short-term (<1 year) insulin independence.¹⁰⁹⁻¹¹¹ The Edmonton protocol prescribed transplanting a large number of freshly isolated islets (>10,000 islet equivalents per kilogram body weight, typically requiring the use of two to four pancreases) with a specialized “islet-sparing,” steroid-free immunosuppressive protocol consisting of low-dose tacrolimus, sirolimus, and IL-2 receptor antibody induction. Those results were replicated at other experienced transplant centers,^{112,113} but the rates of long-term (>5 year) insulin independence remained poor, well below those of whole-pancreas transplants.¹¹⁴ Still, despite the low rates of long-term insulin independence, most

islet recipients were C-peptide positive and retained hypoglycemia awareness, indicating residual islet function and benefit. In fact, at 9 years posttransplant, 15% remained insulin-independent, and 73% had hypoglycemia awareness and corrected hemoglobin A_{1c} levels.¹¹⁵

In the mid-2000s, new trials began with the goal of establishing protocols that enable insulin independence, using islets from a single donor pancreas; the results were good, especially with strict donor and recipient selection.^{116,117} In the most experienced centers, long-term rates of diabetes reversal are now about 50% at 5 years posttransplant. The reasons include refinements in pancreas preservation, islet isolation, and culture protocols, as well as the use of newer induction immunosuppressive agent combinations, such as a T-cell-depleting antibody (anti-CD3 antibody, alemtuzumab, or antithymocyte globulin) and a tumor necrosis factor-alpha (TNF- α) inhibitor (etanercept or infliximab). Presumably, viable β -cell mass is now preserved, both pre and posttransplant.¹¹⁶⁻¹²⁰ Thus, islet transplant results are approaching those of whole-pancreas transplants; however, because islets from more than one pancreas are typically needed, those results cannot be directly compared with the results of whole-pancreas transplants.^{121,122}

In the United States, an islet transplant is still officially deemed an experimental procedure. In contrast, since 2001, it has been considered a standard of care and is fully reimbursed in Canada and, more recently, in the United Kingdom, Sweden, Switzerland, France, and Italy as well. Worldwide, since 2000, more than 750 patients with diabetes have undergone an islet transplant, and 80 ongoing trials have enrolled up to 1500 islet recipients.¹¹⁸ One of the U.S. trials (a multicenter phase 3 registration trial sponsored by the National Institutes of Health) aims to collect the necessary data for submitting a biological license application (BLA) to the FDA. A successful BLA would open the road for islet transplants to become a standard of care and thus reimbursable by the Centers for Medicare and Medicaid Services.

The full potential of islet transplants remains to be realized, but the future is exciting. As the latest improvements in pancreas preservation, islet isolation and purification, islet culture, and islet immunoisolation are implemented clinically, the hope is that sustained insulin independence will become consistently possible with a single pancreas donor and without the need for systemic immunosuppression.

LIVER TRANSPLANTATION

The first attempts at liver transplants in the late 1960s through the 1980s were largely experimental endeavors, with a 1-year survival rate of only 30%. But breakthroughs in immunosuppression, surgical technique, organ preservation, anesthesia, and critical care have improved that rate to approximately 85% today. Liver transplants remain daunting, especially in the face of an organ shortage that results in sicker potential candidates. Unfortunately, the perioperative mortality rate and the 1-year mortality rate are among the highest of any surgical operation currently performed.

History

The first experimental liver transplants in dogs are often attributed to C. Stuart Welch in 1955 and then Jack Cannon in 1956. However, current scholarship reveals that Vittorio Staudacher first described the technique in 1952.¹²³ A series of canine

experiments followed, which refined the surgical technique to ensure perioperative survival.

The next obstacle—immunologic rejection—was addressed by drug immunosuppression with AZA and prednisone. The first human liver transplant trials started in 1963 with Thomas Starzl, but a series of deaths led to a voluntary moratorium for 3.5 years. With the resumption of clinical transplants in 1967, Starzl performed the first successful liver transplant. Still, for the next decade, survival rates were dismal: only 20% of the 170 liver transplant recipients in Starzl's program at the University of Colorado survived more than 5 years.¹²⁴

Several innovations dramatically improved outcomes. The advent of better immunosuppressive drugs was instrumental. In 1978, cyclosporine was introduced clinically in England. It was soon combined with prednisone to great effect. The arrival of tacrolimus in the 1990s further improved graft survival.

Technical advances were also significant. Donor procurement techniques and cold organ preservation protocols were standardized, and the recipient operation was also refined. Choledochocholedochostomy or choledochojejunostomy to a Roux-en-Y limb became standard and significantly decreased the frequency of biliary complications. Innovations, including living donor liver transplants and deceased donor split-liver transplants, enabled more pediatric recipients to be transplanted. Improvements in portosystemic shunting and perioperative critical care also were contributory.

Indications

In general, any form of irreversible liver disease is an indication **7▶** for a liver transplant. Chronic alcoholic disease and HCV are the most common indications in the United States. An extensive list of acute and chronic diseases of the liver that are treatable by a liver transplant is provided in Table 11-6.

Offering transplants to alcoholic patients has always drawn some opposition, because of the perception of it being a self-inflicted illness, as well as concerns about recidivism and the recipient's possible inability to maintain postoperative immunosuppression and care. Yet studies have shown that such patients have excellent outcomes and that liver transplants for them are cost-effective.¹²⁵⁻¹²⁷ Because patients who drink 4 to 8 ounces of liquor daily for 10 to 15 years have an increased risk of developing cirrhosis, the general requirement for acceptance as a transplant candidate is 6 months of abstinence. Furthermore, most transplant centers recommend rehabilitation and Alcoholics Anonymous programs.

Transplants for HCV have yielded worse outcomes than transplants for other diseases.¹²⁸ The reason is the universal recurrence of the virus posttransplant. Viral levels reach pretransplant levels as early as 72 hours posttransplant.¹²⁹ The course of the viral infection is often accelerated posttransplant: 10% to 20% of recipients develop cirrhosis after just 5 years.¹³⁰ Studies have suggested that use of older donors may increase the chance of aggressive recurrence.¹³¹ The best method to prevent recurrence would be to eradicate the infection pretransplant, but doing so is not always possible because patients with decompensated cirrhosis often cannot tolerate treatment. Once recurrence occurs, treatment methods are limited. One study found that pegylated interferon and ribavirin therapy achieved a sustained viral response in 44% of patients.¹³²

A substantial number of patients undergo liver transplants for cholestatic disorders. Primary biliary cirrhosis, an autoimmune disease, is characterized by damage to the intralobular bile

Table 11-6

Diseases amenable to treatment by a liver transplant

Autoimmune liver diseases
Autoimmune hepatitis
Primary biliary cirrhosis
Primary sclerosing cholangitis
Congenital
Biliary atresia
Viral hepatitis
Hepatitis B
Hepatitis C
Alcoholic liver disease
Metabolic diseases
α_1 -Antitrypsin deficiency
Cystic fibrosis
Hemochromatosis
Tyrosinemia
Wilson's disease
Hepatic malignancy
Hepatocellular carcinoma
Neuroendocrine tumor metastatic to liver
Fulminant hepatic failure
Other
Alagille syndrome
Cryptogenic cirrhosis
Budd-Chiari syndrome
Polycystic liver disease
Amyloidosis

ducts that progresses to liver cirrhosis. Trends toward earlier treatment may explain the slight decrease in liver transplants for this disorder.¹³³ Posttransplant outcomes in patients with this disorder have been excellent, with many centers achieving 1-year survival rates of 90% to 95%. Recurrence is relatively uncommon: a large series reported a 30% recurrence rate at 10 years posttransplant.¹³⁴

The second most common cholestatic disorder among liver transplant candidates is primary sclerosing cholangitis. It is characterized by inflammation and fibrosis of large intra- and extrahepatic biliary ducts; 70% of such patients also have inflammatory bowel disease. Recurrent cholangitis is common and increases mortality rates beyond what would be expected on the basis of laboratory values. On behalf of such patients, appeals can often be made for priority in allocation to the UNOS regional review boards. Posttransplant outcomes for such patients have been excellent. Primary sclerosing cholangitis is a significant risk factor for cholangiocarcinoma, so annual screenings (including imaging and measurement of serum CA 19-9 levels) should be carried out. Recurrence is fairly uncommon: studies have reported a recurrence rate of up to 20% at 10 years posttransplant.¹³⁵

Progressive metabolic disorders also are treatable with liver transplants. Hemochromatosis, an inherited disorder, results in excessive intestinal iron absorption. Iron deposition can cause cirrhosis and severe cardiomyopathy. Careful cardiac evaluation is necessary pretransplant.

Another metabolic disorder, α_1 -antitrypsin deficiency, is characterized by insufficient levels of a protease inhibitor,

resulting in early-onset emphysema and cirrhosis. Careful pulmonary evaluation is necessary pretransplant.

Wilson's disease, an autosomal recessive disorder characterized by impaired cellular copper transport, leads to copper accumulation in the liver, brain, and cornea. Patients can develop significant neurologic complications and cirrhosis. Several reports suggest improvement of neurologic deficiencies posttransplant.^{136,137}

Transplants can also be performed in patients with hepatic malignancies, but only in accordance with strict criteria. Hepatocellular carcinoma (HCC), a complication of cirrhosis, is the most common type of hepatic malignancy. Resection is the first line of treatment if possible, but often, cirrhosis is too advanced. If the tumor meets the Milan criteria, a liver transplant can be performed. These criteria were established by a landmark paper in 1996 showing that patients with a single tumor under 5 cm in diameter, or with three tumors under 3 cm in diameter, in the absence of vascular invasion, had a 4-year survival rate of 85%.¹³⁸ Patients with such tumors receive exception points, based on their UNOS region, allowing for a timely transplant before their tumors spread.

Transplants for cholangiocarcinoma are still in the experimental stages but may be performed if the center has an experimental protocol in place. The Mayo Clinic protocol, which uses neoadjuvant therapy and strict exclusion criteria, has resulted in a 5-year survival rate of 82%.¹³⁹

Acute fulminant hepatic failure also is an indication for a liver transplant; in fact, such patients are the highest priority for the next available liver in their UNOS region. This devastating illness is defined by acute and severe liver injury with impaired synthetic function and encephalopathy in a person who had normal liver function. It is often caused by acetaminophen overdose; acute fulminant viral hepatitis A, B, and E; other viral infections; drug toxicity; ingestion of *Amanita* mushrooms; acute fatty liver of pregnancy; or Wilson's disease. A significant number of patients will recover with supportive care. The difficulty lies in predicting who will *not* recover and therefore would benefit from a liver transplant. The King's College criteria were developed for this purpose: patients with acetaminophen-induced disease, a pH <7.3 or grade III/IV encephalopathy, a prothrombin time >100 seconds, and serum creatinine >3.4 mg/dL meet those criteria.¹⁴⁰ Management of acute liver failure is very intensive. Such patients suffer from severe coagulopathy, hypoglycemia, lactic acidosis, and renal dysfunction. They are susceptible to infections, which are frequently overwhelming. Cerebral edema, a serious complication of acute liver failure, is a leading cause of death from brain herniation. Intracranial pressure monitoring and serial imaging are often necessary; if a patient develops irreversible brain damage, a transplant is not performed.

Recipient Selection

The diagnosis of cirrhosis itself is not an indication for a transplant. Patients may have compensated cirrhosis for years such that the traditional indication for a transplant is decompensated cirrhosis, manifested by hepatic encephalopathy, ascites, spontaneous bacterial peritonitis, portal hypertensive bleeding, and hepatorenal syndrome (each described below).

Hepatic encephalopathy is an altered neuropsychiatric state caused by metabolic abnormalities resulting from liver failure. The early stages result in sleep disturbances and depression. As the liver disease progresses, patients can become somnolent

and confused and, in the end stages, comatose. Ammonia is produced by enterocytes from glutamine and from colonic bacterial catabolism, and the use of serum ammonia levels as a marker of encephalopathy is controversial because a variety of factors can influence levels. Hyperammonemia suggests worsening liver function and bypass of portal blood flow around the liver. GI bleeding and infection can exacerbate hepatic encephalopathy.

Ascites (the accumulation of fluid in the abdominal cavity) that is caused by cirrhosis is a transudate with a high serum-ascites gradient (>1.1 g/dL). Associated with portal hypertension, it is treated initially with sodium restriction and diuretics. Refractory ascites necessitates large-volume paracentesis and eventually a transjugular intrahepatic portosystemic shunt (TIPS). Contraindications to TIPS placement include significant hepatic encephalopathy, advanced liver disease, congestive heart failure, renal insufficiency, and severe pulmonary hypertension.¹⁴¹

Spontaneous bacterial peritonitis, an infection of the ascitic fluid without an evident intra-abdominal source, is characterized by fever, abdominal pain, and an ascitic fluid polymorphonuclear count ≥ 250 cell/mm³ on paracentesis. The first line of empiric treatment is with a third-generation cephalosporin because the majority of cases are caused by aerobic gram-negative microbes such as *E. coli*, although Gram stain and culture results should be used to guide therapy.

Portal hypertensive bleeding can be a devastating event for patients with cirrhosis. Each bleeding event carries a 30% mortality rate and accounts for a third of all deaths related to cirrhosis. Only 50% of bleeding events cease spontaneously, so treatment must be expedient. The initial medical treatment is with vasopressin and octreotide. The initial intervention is endoscopy with sclerotherapy and band ligation of bleeding varices. If those initial attempts fail, more aggressive treatment is necessary with a balloon tamponade (using a Sengstaken-Blakemore tube) and with emergent TIPS placement. The last line of treatment is emergency surgery to place a portosystemic shunt, transect the esophagus, or devascularize the gastroesophageal junction (Sugiura procedure). Preventing variceal bleeding is essential and can be achieved, with some success, using β -blockers.

Hepatorenal syndrome is a form of acute renal failure that develops as liver disease worsens. The etiology is unclear, but splanchnic vasodilation from portal hypertension and increased production of circulating vasodilators result in a decline in renal perfusion. Characterized by oliguria (<500 mL of urine/day) and low urine sodium levels (<10 mEq/L), hepatorenal syndrome is often reversed by a liver transplant, even after dialysis dependence. Pretransplant, other causes of renal failure need to be excluded, including ATN, drug nephrotoxicity, and chronic renal disease. The initial medical therapy includes octreotide, midodrine, and vasopressin analogs, but the syndrome often progresses to dialysis dependence.

The Model for End-Stage Liver Disease (MELD) was originally developed to assess risk for TIPS placement.¹⁴² Later analysis revealed it to be an excellent model to predict survival among patients with cirrhosis, especially those on the waiting list for a liver transplant.¹⁴³ In 2002, liver graft allocation was restructured to be based on the MELD score.

Although the historic indication for a liver transplant is decompensated cirrhosis, a landmark analysis comparing waiting list mortality with posttransplant mortality established that a minimum MELD score of 18 is necessary to have a survival benefit posttransplant. A MELD score between 15 and 18 does

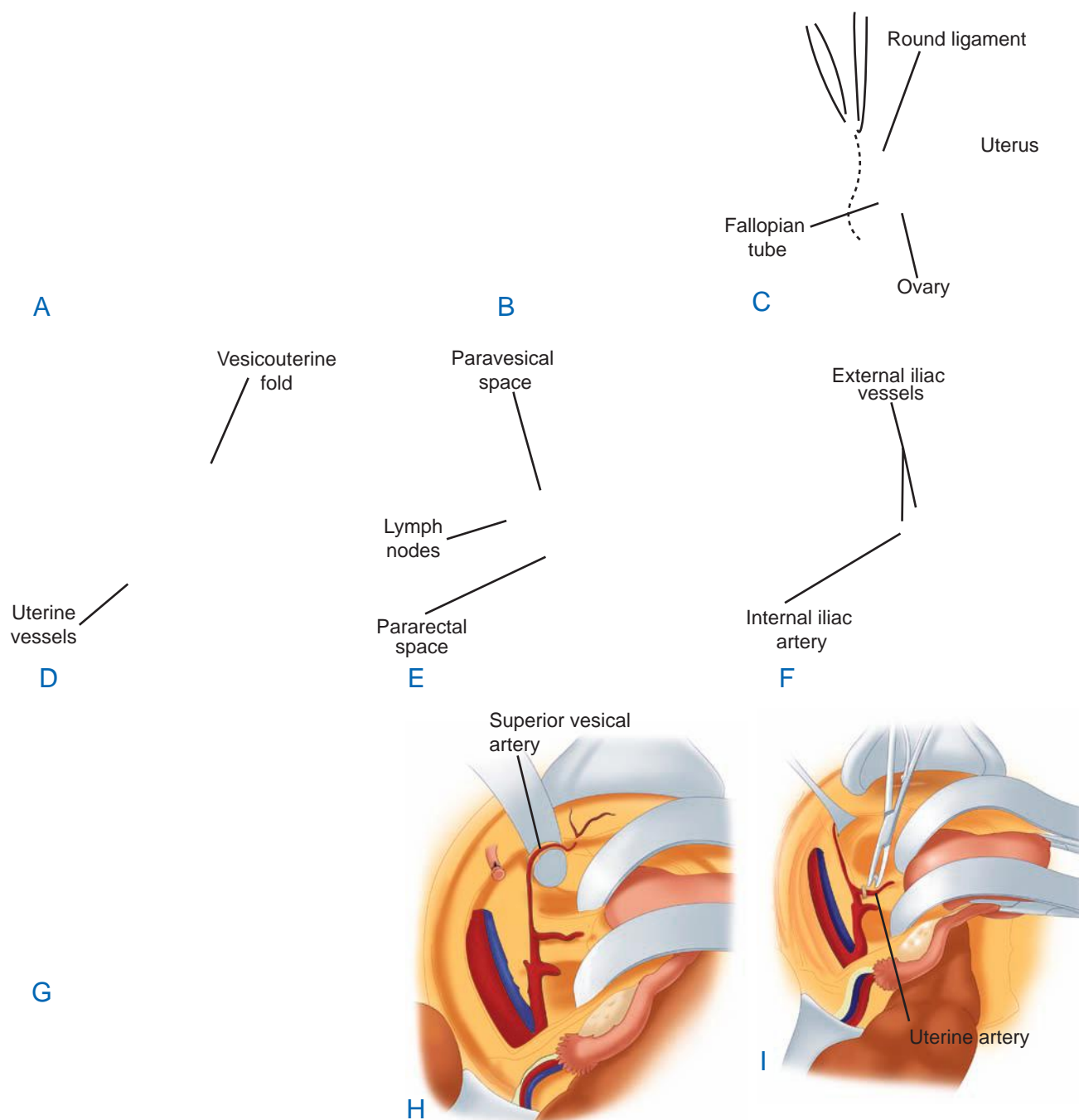


Figure 41-21. Radical hysterectomy. **A.** Exposure of the inferior epigastric vessels before transection of the rectus muscles. **B.** Ligation of the inferior epigastric vessels before transection of the rectus muscles. **C.** Ligation and division of the round ligaments opens the pelvic retroperitoneum. **D.** First peritoneal incision lateral to the ovarian vessels and across the vesicouterine fold. **E.** Narrow malleable retractors (Indiana retractors) are placed into the paravesical and pararectal spaces to provide excellent access to the lateral pelvic sidewall and pelvic lymph nodes. **F.** Pelvic lymphadenectomy (external and internal iliac vessels). **G.** Pelvic lymphadenectomy (obturator fossa). **H.** Development of the uterine and superior vesical arteries. **I.** The uterine artery has been clipped and divided near its origin. **J.** The proper ovarian ligament and proximal fallopian tube are clamped and divided if the ovary is to be preserved. **K.** The ureters have been detached from the posterior peritoneum of the broad ligament and are retracted laterally. The rectovaginal space is developed using blunt finger dissection. **L.** Transection of the uterosacral ligaments. **M.** Clamps are placed on the lateral vagina, taking care to remove 3 to 4 cm of the upper vagina.

women.⁶⁶ It is most common in menopausal women in the fifth decade of life; up to 15% to 25% of cases occur prior to menopause, and 1% to 5% occur before age 40. Risk factors for the most common type of endometrial cancer include increased exposure to estrogen without adequate opposition by progesterone, either endogenous (obesity, chronic anovulation) or exogenous (hormone replacement). Additional risk factors

include diabetes, Lynch II syndrome (hereditary nonpolyposis colorectal cancer), and prolonged use of tamoxifen. Tamoxifen is a mixed agonist/antagonist ligand for the estrogen receptor. It is an agonistic in the uterus and an antagonistic to the breast and ovary. Protective factors for endometrial cancer include smoking and use of combination oral contraceptive pills. Adenocarcinomas are the most prevalent histologic type.

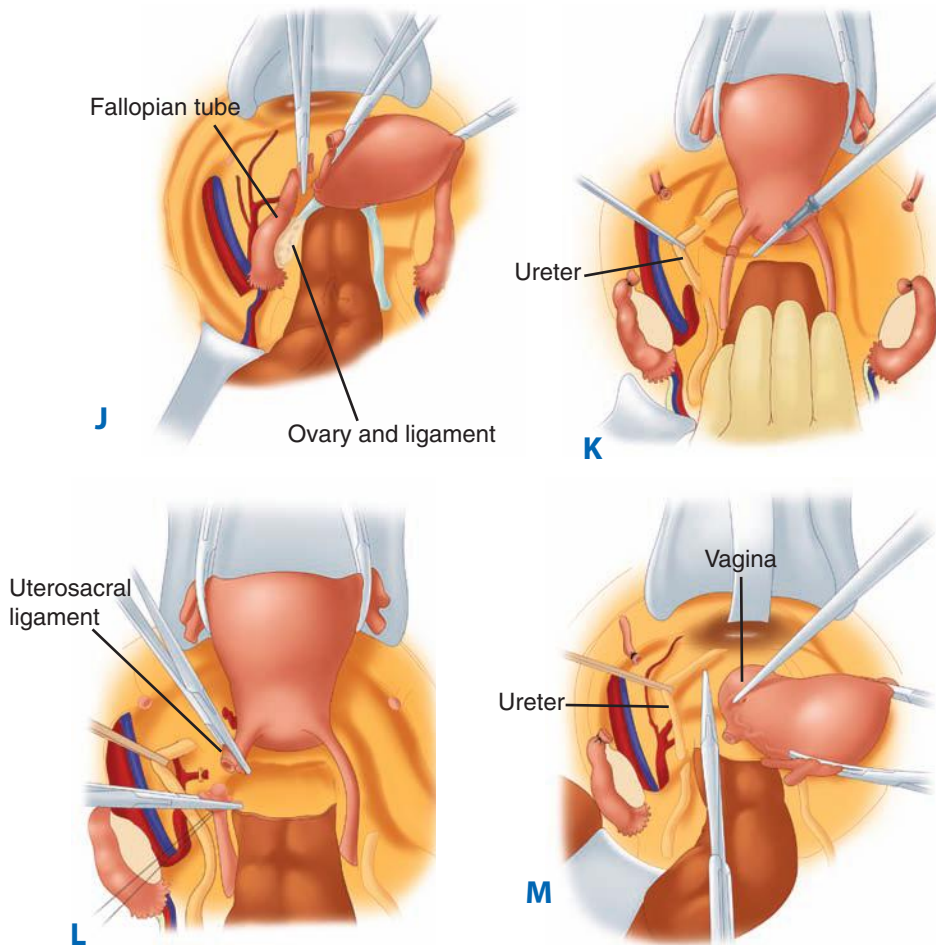


Figure 41-21. (Continued)

Endometrial adenocarcinomas are divided into type I and type II, although there is a trend to return to histology as a divider. Type I tumors are estrogen-dependent endometrioid histology and have a relatively favorable prognosis. Type II endometrial cancers are estrogen-independent, aggressive, and characterized by nonendometrioid, serous, or clear cell histology.⁸¹ Postmenopausal bleeding is the most common presentation of type I disease and often permits early-stage diagnosis,

resulting in a favorable prognosis. Abnormal bleeding should prompt endometrial evaluation and sampling, which is usually done with an office endometrial biopsy, although at times, it requires operative curettage or diagnostic hysteroscopy. Transvaginal ultrasonography (TVUS) often reveals a thickened endometrial stripe. An endometrial stripe measuring 5 mm or more in a postmenopausal patient raises concern and should be followed by endometrial sampling; patients with stripe of 4 mm

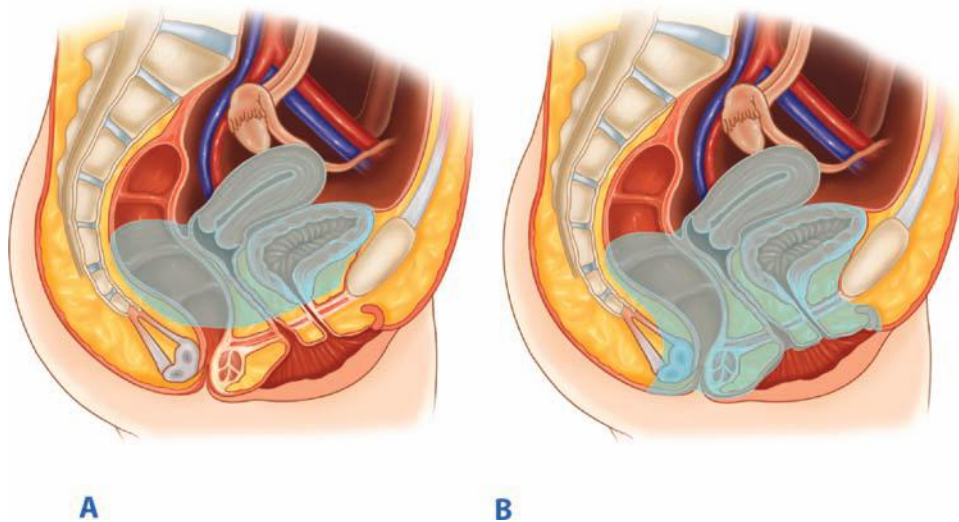


Figure 41-22. Pelvic exenteration may be limited to the supralelevator space (A) or can extend below the levator ani muscle (shaded area) (B).

Table 41-9

2009 International Federation of Gynecology and Obstetrics staging of carcinoma of the uterine corpus⁷⁸

IA	Tumor confined to the uterus, no or <½ myometrial invasion
IB	Tumor confined to the uterus, >½ myometrial invasion
II	Cervical stromal invasion, but not beyond uterus
IIIA	Tumor invades serosa or adnexa
IIIB	Vaginal and/or parametrial involvement
IIIC1	Pelvic node involvement
IIIC2	Para-aortic involvement
IVA	Tumor invasion bladder and/or bowel mucosa
IVB	Distant metastases including abdominal metastases and/or inguinal lymph nodes

or less rarely have occult malignancy, and TVUS may thus be used to triage patients before invasive endometrial sampling. Uterine cancer is surgically staged and is graded based on the degree of histologic differentiation of the glandular components (Table 41-9).⁷⁸ Grade is an important prognostic factor, independent of stage.

Treatment is surgical and most commonly involves hysterectomy, bilateral salpingo-oophorectomy, peritoneal cytology, pelvic and para-aortic lymphadenectomy, and resection of any gross disease.^{68,69,75} Evidence supports equivalent oncologic outcomes with minimally invasive approaches.⁸² The utility of lymphadenectomy is an area of great controversy. The need for postoperative adjuvant radiation or chemotherapy is individualized based on the histology, stage, and risk factors such as age, lymphovascular space invasion, and histology. Early-stage patients are typically cured with surgery alone, whereas patients with high- or intermediate-risk factors, as defined by collaborative trials groups, commonly receive intracavitary brachytherapy to decrease local recurrence.^{83,84} Patients with advanced disease and adverse histologies commonly receive platinum-based chemotherapy with or without radiation.

Lynch Syndrome. Lynch syndrome, a cancer family syndrome, also known as hereditary nonpolyposis colorectal cancer (HNPCC), is an autosomal dominant inherited predisposition to develop colorectal carcinoma and extracolonic cancers, predominantly including tumors of the uterus and ovaries, with rare but defined inclusion of breast cancer.⁸⁵ Genes involved in HNPCC are those required for proper single-strand DNA repair via the mismatch repair pathway; most commonly involved are *MLH1*, *MSH2*, and *MSH6*. The risk of colorectal carcinoma is as high as 75% by age 75. Affected female patients have a 40% and 10% lifetime risk of developing uterine and ovarian cancers, respectively. Surveillance has not been proven to identify early-stage disease in these patients, although it is recommended and should include annual cervical cytology, mammography, transvaginal ultrasonography, CA-125 measurements, and an endometrial biopsy. Risk reduction salpingo-oophorectomy with hysterectomy is now being recommended for women who have completed childbearing, ideally 5 to 10 years earlier than the first case of endometrial or ovarian cancer in the family.

Uterine Sarcomas. Uterine sarcomas arise from the uterine muscle and connective tissue elements and are typically aggressive tumors with a poorer prognosis compared to the

more common endometrial carcinomas. The most common histopathologic types are endometrial stromal sarcomas, undifferentiated endometrial sarcomas, and leiomyosarcomas. Risk factors are challenging to assess but may include African American race, pelvic radiation, and tamoxifen exposure. Patients typically present with bleeding or mass effects, although some are discovered incidentally at the time of hysterectomy for other indications. Leiomyosarcoma is the most common uterine sarcoma, and hysterectomy with salpingo-oophorectomy is the treatment of choice. Lymph node metastases are rare in sarcomas in general, and in uterine sarcomas in the absence of palpable nodes or extrauterine disease. There are limited data to support cytoreduction when extrauterine disease is present. Benefits of adjuvant therapy are unknown. Advanced disease is typically treated with systemic chemotherapy.⁸⁶

Ovarian, Tubal, and Primary Peritoneal Cancer

Epithelial Ovarian, Tubal, and Primary Peritoneal Cancer.

There were an estimated 22,280 new cases and 15,500 deaths due to ovarian cancers in 2012, yielding a fractional death rate of 70% and making ovarian cancer the most deadly of all women's cancers.⁶⁶ One in 60 to 70 women in the United States will develop ovarian cancer during her lifetime, with a median age at diagnosis of 63 years. Symptoms for either benign or malignant ovarian tumors are nonspecific but frequent. Goff and colleagues, in a 2007 publication, described symptoms of bloating, pelvic or abdominal pain, difficulty eating or feeling full quickly, and urinary symptoms of urgency or frequency,⁸⁷ which form the basis of an ovarian cancer symptom index (Table 41-10), the use of which is endorsed by the Ovarian Cancer National Alliance, the Gynecologic Cancer Foundation, the Society of Gynecologic Oncologists, and the American Cancer Society. These symptoms, when newly developed and persistent or when representing a distinct change from a personal norm, should prompt an evaluation specifically targeted for identification of gynecologic malignancy.

High-grade, particularly serous epithelial cancers of the ovary, fallopian tube, and peritoneum are clinically similar and often combined under the rubric of epithelial ovarian cancer (EOC) in clinical practice, as well as in research and clinical trials. Risk factors for development of EOC include events that appear to increase the number of lifetime ovulations (e.g., early menarche, late menopause, nulliparity), whereas events that decrease the number of ovulations decrease risk (e.g., pregnancy, breastfeeding, oral contraceptives). Additionally, a history of tubal ligation or hysterectomy also decreases EOC risk. Family history of breast cancer and/or EOC is one of the strongest factors for lifetime risk of having breast cancer or EOC. Approximately 85% of ovarian cancer is sporadic; of the remaining 10% of cases, 75% of hereditary ovarian cancer has been attributed to mutations in the *BRCA1* and *BRCA2* genes, 7% to HNPCC, and the remainder to familial cancer of undefined genetic origin.⁸⁸ The lifetime risk of ovarian cancer in *BRCA1* mutation carriers has been estimated at 40% to 60%, and it is 15% to 45% in *BRCA2* carriers. The only confirmed

9► prevention is risk-reducing salpingo-oophorectomy (RRSO).^{89,90} The lifetime risk of ovarian or tubal malignancy is reduced to approximately 5% with RRSO, with the resultant cancer presenting as a primary peritoneal cancer.

Physical examination of patients with EOC may reveal evidence of metastatic disease, whereas a pelvic mass may be

Table 41-10

Ovarian cancer symptom index (2007) and ACOG guidelines for patient referral to gynecologic oncology^{87, 104}

OVARIAN CANCER SYMPTOM INDEX	ACOG GUIDELINES FOR REFERRAL OF PREMENOPAUSAL WOMEN WITH MASS SUSPICIOUS FOR OVARIAN CANCER	ACOG GUIDELINES FOR REFERRAL OF POSTMENOPAUSAL WOMEN WITH MASS SUSPICIOUS FOR OVARIAN CANCER
<i>Development of, change in, and/or persistence in:</i>	<i>1 or more of:</i>	<i>1 or more of:</i>
Bloating	CA-125 >200 U/mL	Elevated CA-125
Pelvic or abdominal pain	Ascites	Ascites
Difficulty eating or feeling full quickly	Evidence of abdominal or distant metastasis	Nodular or fixed pelvic mass
Urinary symptoms of urgency or frequency	Family hx of 1 or more first-degree relatives with ovarian or breast cancer	Evidence of abdominal or distant metastasis
		Family hx of 1 or more first-degree relatives with ovarian or breast cancer

ACOG = American Congress of Obstetricians and Gynecologists; hx = history.

appreciated on exam. Ultrasound is particularly useful in the evaluation of a pelvic mass, whereas CT scan may detect evidence of metastatic disease. In the presence of a radiographically complex mass, CA-125 may provide further evidence for or against a possible ovarian malignancy. Concerning physical or radiographic exam findings should prompt referral to a gynecologic oncologist (see Table 41-10), as studies demonstrate inferior patient outcomes for women who have had primary surgery by nongynecologic oncologists.

The objectives of surgery in EOC are threefold. The first is to make the histologic diagnosis. The second is to assess the extent of disease through complete surgical staging (Tables 41-11 and 41-12). The third objective is (complete when feasible) surgical cytoreduction or debulking. An optimal cytoreduction is defined as no gross residual lesion greater than 1 cm, although

outcomes are improved with complete resection of all gross disease. The extent of disease upon entering the abdomen and the residual disease upon completion of the debulking surgery are independent prognostic variables for patient outcome. When EOC is identified on frozen section and disease is grossly limited to the pelvis, complete staging with node dissection will upstage nearly one third of patients.⁹¹ Decisions about the benefits and risks of radical debulking for individual presentations and diverse pathology depend on the age and medical stability of the patient, as well as the pathologic type of the cancer. Conservative, fertility-sparing surgery can be considered for likely stage I, grade 1 EOC. In a patient who is medically compromised or in whom complete primary cytoreduction is unlikely, neoadjuvant chemotherapy followed by interval debulking may be more appropriate and is supported by a recent randomized controlled trial.⁹² Patients usually receive three cycles of platinum-based chemotherapy prior to debulking, and then three additional cycles after surgery.

Early-stage EOC has an excellent outcome. Low-grade, stage IA and IB disease can be cured in up to 90% to 95% of cases by a complete surgical procedure. The prevailing position in the United States is that such patients do not benefit from

Table 41-11

Risk and protective factors for epithelial ovarian and fallopian tube cancers

PROTECTIVE FACTORS	RISKS
Oral contraceptive use, especially >5 years	Primary and secondary infertility
Tubal ligation	Nulliparity
Lactation	BRCA1/2 mutation and HNPCC syndrome
Pregnancy	Family history without genetic risk
Oophorectomy, salpingectomy	Endometriosis
	Personal history of breast cancer or first-degree relative with breast cancer
	? Hormone replacement therapy

HNPCC = hereditary nonpolyposis colorectal cancer.

Table 41-12

Components of comprehensive surgical staging and debulking of epithelial ovarian cancer

Vertical abdominal incision adequate to visualize the diaphragms
Evacuation of ascites
Peritoneal washings of each pelvic gutter and diaphragm
En bloc hysterectomy and bilateral salpingo-oophorectomy
Supracolic omentectomy
Retroperitoneal and pelvic lymph node dissection
Examination of the entire bowel
Random biopsies of apparently uninvolved areas of peritoneum, pericolic gutters, diaphragm

chemotherapy.⁹³ The standard of care for women with stages IC and II and all women with grade 3 or clear cell histology is adjuvant chemotherapy with three to six cycles of cisplatin or carboplatin in combination with paclitaxel or docetaxel.⁹⁴

Since GOG-111⁹⁵ was published in 1996, and through much of the subsequent decade, standard-of-care adjuvant therapy of advanced-stage EOC has been intravenous (IV) platinum and taxane. More recent trials have sustained that chemotherapy backbone but prompt an individualized, more nuanced approach. In 2006, the National Cancer Institute issued a Clinical Alert indicating that inclusion of intraperitoneal chemotherapy administration in adjuvant therapy should be considered first line for women with optimally cytoreduced (defined as no residual lesions >1 cm in diameter) EOC. This was the result of completion and analysis of three independent randomized clinical trials showing a significant survival advantage for intraperitoneal therapy.^{96,97} It is unclear whether it is the site of drug administration and/or the doses and dose density used that contributed to the improved outcomes. The intraperitoneal port is usually a 9.6-French venous catheter, with the port placed over the right or left costal margin. The catheter is tunneled caudad with insertion through the fascia in the lower abdomen and the tip in the pelvis.

Patients who have suboptimally debulked advanced-stage disease and/or who are not candidates for intraperitoneal therapy should receive IV adjuvant chemotherapy. Interest has increased in both dose-dense IV chemotherapy dosing as well as incorporation of biologic agents. The Japanese Gynecologic Oncology Group phase III trial of carboplatin and weekly, dose-dense paclitaxel demonstrated significant improvement in both progression-free and overall survival⁹⁸; the U.S. study of this regimen is now maturing. Addition of the angiogenesis inhibitor, bevacizumab, to the standard carboplatin-paclitaxel backbone and its continuance in maintenance therapy provided a modest increase in progression-free survival without an overall survival advantage. Patients with bulky disease after primary surgery appeared to derive the greatest benefit in post-hoc analysis.^{99,100}

Secondary cytoreduction upon recurrence can be considered (Table 41-13). Patients who have had a disease-free period of at least 12 months, following an initial complete clinical

response to surgery and initial chemotherapy, who have no evidence of carcinomatosis on imaging, and who have disease that can be completely resected are considered optimal candidates. A randomized controlled trial is ongoing to validate that current state of treatment. Debulking surgery done after subsequent relapses or in women with early recurrence has not been shown to result in an outcome benefit. Finally, surgery is used to palliate disease complications. The most common cause of palliative surgery is bypass of bowel obstruction.

Chemotherapy is the mainstay of therapy for recurrent EOC. Treatment approaches are based on platinum sensitivity¹⁰¹ (Table 41-14). Referral to an oncologist with specific expertise in chemotherapeutic treatment of ovarian cancer and access to clinical trials is important. In determining secondary and subsequent therapy, consideration of prior therapies, sites of disease, organs at risk from cancer, organs sustaining injury from prior therapy, and quality of life desires of the patient should be taken into consideration.

Ovarian Germ Cell Tumors. Ovarian germ cell tumors occur most commonly in women under age 30. Malignant forms often grow and disseminate rapidly and are symptomatic. The rapid growth may be accompanied by torsion producing an acute abdomen and need for emergent intervention. Because they are derived from primordial germ cells, many produce characteristic tumor markers. The most common benign germ cell neoplasm is the mature cystic teratoma; approximately 1% of teratomas contain a secondary malignancy arising from one of the components, most commonly squamous cell cancer. Immature teratomas comprise a significant proportion of malignant germ cell tumors and may be associated with elevated lactate dehydrogenase (LDH) or α -fetoprotein (AFP). Excluding teratomas, the most common malignant germ cell tumor is dysgerminoma, made up of pure undifferentiated germ cells. Bilaterality occurs in up to 15% of patients; lactate dehydrogenase is commonly elevated, and elevated β -hCG may occur. Staging, including removal of the involved ovary, biopsy of any suspicious areas, node dissection, and omentectomy, should be done initially but does not require hysterectomy or removal of the second ovary if fertility preservation is of concern and no extension of disease is observed. Evidence of extraovarian spread, such

Table 41-13

Guidelines for secondary debulking of epithelial ovarian cancer

TIME FROM COMPLETION OF PRIMARY THERAPY	DEFINITION	INTERVENTION
Progression on therapy	Platinum-refractory	No value of secondary debulking unless remediating complication such as bowel obstruction Nonplatinum-based chemotherapy Platinum with gemcitabine (class I) Nonplatinum-based chemotherapy
Progression within 6 months of completion of primary therapy	Platinum-resistant	No value of secondary debulking unless remediating complication such as bowel obstruction Nonplatinum-based chemotherapy Platinum with gemcitabine (class I) Nonplatinum-based chemotherapy
Progression 6 months after completion of primary therapy	Platinum-sensitive	Consider secondary debulking if greater than 12-month interval Consider platinum +/- taxane +/- bevacizumab, +/- pegylated liposomal doxorubicin, +/- gemcitabine (class I) Nonplatinum-based chemotherapy

Table 41-14

Definitions of platinum resistance and guidelines for treatment of recurrent disease

PLATINUM SENSITIVITY	DEFINITION	INTERVENTION
Refractory	Progression while receiving a platinum	Nonplatinum-based chemotherapy Platinum with gemcitabine
Resistant	Progression within 6 months of completing treatment	Nonplatinum-based chemotherapy Platinum with gemcitabine
Sensitive	Progression after 6 months of completing treatment	Consider secondary debulking if >12 months since treatment Consider platinum \pm taxane Nonplatinum-based chemotherapy

as nodal metastases, requires adjuvant chemotherapy. The cure rate remains high, near 90% with metastatic disease; recurrent disease is more difficult to eradicate.¹⁰²

Less common are malignant germ cell tumors, including endodermal sinus or yolk sac tumors, embryonal carcinomas, mixed germ cell neoplasms, polyembryomas, and choriocarcinomas. Endodermal sinus tumors may have elevated AFP levels in the blood, whereas embryonal and mixed germ cell tumors may have elevated β -hCG, LDH, or AFP. Tumor markers are useful to follow during definitive therapy. Early spread of these tumors occurs, and other than completely resected stage I, grade 1 immature teratoma, all others require adjuvant therapy with a platinum-containing regimen.¹⁰³

Ovarian Sex Cord-Stromal Tumors. Although rare, sex cord-stromal cell tumors are derived from cells that support and surround the oocyte and can present with symptoms referable to endocrine activity of the tumor. These include granulosa cell tumors (female differentiated), fibroma-thecomas, and Sertoli-Leydig cell tumors (male differentiated). Granulosa cell tumors are the most common in this group and are a low-grade malignancy with less than 3% bilaterality. They are treated with conservative surgery, similar to germ cell tumors in young women.¹⁰³ Hysterectomy and bilateral salpingo-oophorectomy are recommended for women who have completed childbearing. Nodal staging can be safely omitted in the absence of grossly involved nodes, and fertility preservation is possible in disease limited to one ovary, the most common presentation. Debulking surgery is recommended for more extensive disease. These tumors and the thecomas in the same class often stimulate estrogen production and can be found in association with endometrial hyperplasia and cancer (5%). Granulosa cell tumors can recur over a prolonged period given their low rate of proliferation and tendency for local or intraperitoneal recurrence. Inhibin has been shown to be elaborated by these tumors and often is followed to identify recurrence of the disease. The Sertoli-Leydig cell tumors can present with virilization as a primary symptom. Evaluation of the ovary when this symptom is found is always of value.

MINIMALLY INVASIVE GYNECOLOGIC SURGERY

Hysteroscopy

See earlier section, Hysteroscopy, under Procedures Performed for Structural Causes of Abnormal Uterine Bleeding.

Laparoscopy

The standard method for gynecologic laparoscopy follows the same methods as all minimally invasive surgery. In general, a camera port is placed near the umbilicus. Sometimes it must be placed more cephalad if the patient has a larger fibroid uterus. Two additional ports are placed laterally, usually just superior and medial to the anterior superior iliac spines (ASIS). Sometimes one additional suprapubic port is placed for extra traction or instrumentation as described elsewhere in this text.

Complications Related to Gynecologic Surgery

Abdominal Wall Vessels. The vessel at greatest risk of injury during the lateral trocar placement is the inferior epigastric artery. The superficial epigastric vessels and the superficial circumflex iliac vessels can be injured as well (Fig. 41-23). The primary methods to avoid vessel injury are knowledge of the vessels at risk and their visualization prior to trocar placement, when possible. The superficial vessels often can be seen and avoided by transillumination of the abdominal wall with the laparoscope. In contrast, the larger inferior epigastric vessels cannot be seen by transillumination because of their deeper location; these vessels often can be seen laparoscopically and avoided as they course along the peritoneum between the lateral umbilical fold of the bladder and the insertion of the round

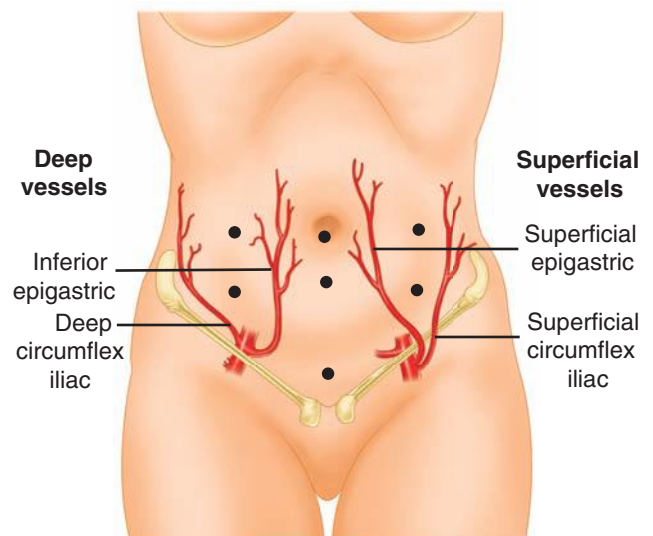


Figure 41-23. Location of anterior abdominal wall blood vessels.

ligament into the inguinal canal. Anatomic variation and anastomoses between vessels make it impossible to know the exact location of all the abdominal wall vessels. For this reason, other strategies also should be used to avoid vessel injury, including the use of trocars with conical tips rather than pyramid tips and the use of the smallest trocars possible lateral to the midline.

Intestinal Injury. Another potentially serious complication of laparoscopic surgery is injury to either small or large intestines. An unrecognized bowel injury may occur at the time of trocar insertion, especially if the patient has had previous abdominal procedures that often result in bowel adhesions to the anterior abdominal wall peritoneum. An open technique for placement of the first port is advocated to minimize the risk of bowel injury in patients who have undergone previous laparotomy. Some bowel injuries may not be seen during surgery because of the limited field of view. These injuries usually manifest 1 to 3 days after surgery, well after the patient has been released following these primarily outpatient procedures, and any patient concerns in this time period should be addressed seriously and rapidly.

Urologic Injuries. Bladder injury is an uncommon laparoscopic injury, occurring as a result of retroperitoneal perforation during lower trocar placement or during sharp dissection of the bladder from the lower uterine segment during hysterectomy. The latter of these two situations is usually recognized intraoperatively; the first sign of the former may be postoperative hematuria or lower-port incisional drainage. Once diagnosed, large defects require layered closure, whereas smaller defects usually close spontaneously within days or weeks with the aid of transurethral catheter drainage. Ureteral injury may occur as a result of any procedure that requires dissection or ligation of sidewall vessels, such as removal of adnexa, because the ureter is adjacent to the pelvic peritoneum in the area of the ovarian fossa (see Fig. 41-5). This complication also has been reported after fulguration of endometriosis on the pelvic sidewall. Another common cause of ureteral injury is hysterectomy, because the ureter is often located less than 2 cm from the cervix. This type of injury appears to be increased during laparoscopic hysterectomy, compared to abdominal or vaginal approaches. Ureteral injuries, including complete ligation, partial resection, or thermal injuries, usually will manifest within hours to days of surgery. Complete obstruction most often manifests as flank pain, whereas the first sign of partial or complete transection may be symptoms of intra-abdominal irritation caused by urine leakage. Transperitoneal thermal injuries resulting from fulguration of endometriosis may be similar to those after transection, but the appearance of symptoms may be delayed several days until tissue necrosis occurs.

Robotic Surgery

Over the last decade, there has been increased use of robotics for gynecologic surgery. With the DaVinci robotic system, the surgeon sits at a console and visualizes the operative field with three-dimensional optics. The laparoscopic instruments are “wristed” and move as the surgeon’s hands/fingers move the actuators at the console. Robotic surgery uses a camera port, two to three robotic ports, and an accessory port. More meticulous dissection, improved visualization, and ability to operate with lower intra-abdominal pressures make the robotic platform advantageous, especially in obese patients. Longer set-up time and increased cost, however, are distinct disadvantages. The use of robotic surgery has been described for virtually every gynecologic procedure that has been performed abdominally or laparoscopically.

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chapter

Neurosurgery

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OVERVIEW

Neurologic surgery provides the operative and nonoperative management (i.e., prevention, diagnosis, evaluation, treatment, critical care, and rehabilitation) of disorders of the central, peripheral, and autonomic nervous systems (ANSs). Such disorders include those of the brain, meninges, skull and skull base, and their blood supply, including surgical and endovascular treatment of disorders of the intracranial and extracranial vasculature supplying the brain and spinal cord; disorders of the pituitary gland; disorders of the spinal cord, meninges, and vertebral column, including those that may require treatment by fusion, instrumentation, or endovascular techniques; and disorders of the cranial and spinal nerves throughout their distribution.

An accurate history is the first step toward neurologic diagnosis. A history of trauma or of neurologic symptoms is of obvious interest, but general constitutional symptoms are also important. Neurologic disease may have systemic effects, while diseases of other systems may affect neurologic function. The patient's general medical ability to withstand the physiologic stress of anesthesia and surgery should be understood. A detailed history from the patient and/or family, along with a reliable physical examination, will clarify these issues.

NEUROANATOMY

An understanding of neuroanatomy is the foundation of comprehensive neurologic examination and diagnosis. Salient features will be considered, from cephalad to caudad. The cerebral hemispheres (or telencephalon) consist of the cerebral cortex, underlying white matter, the basal ganglia, hippocampus, and amygdala. The cerebral cortex is the most recently evolved part of the nervous system. Its functions are mapped to discrete anatomic areas. The frontal areas are involved in executive function, decision making, and restraint of emotions. The motor strip, or precentral gyrus, is the most posterior component of the frontal lobes, and is arranged along a homunculus with the head inferior and lateral to the lower extremities superiorly and medially. The motor speech area (Broca's area) lies in the left posterior inferior frontal lobe in almost all right-handed people and in up to 90% of left-handed people. The parietal lobe lies between the central sulcus anteriorly and the occipital lobe posteriorly. The postcentral gyrus is the sensory strip, also arranged along a homunculus. The rest of the parietal lobe is involved with awareness of one's body in space and relative to the immediate environment, body orientation, and spatial relationships. The occipital lobes are most posterior. The visual cortex is arrayed along the apposing medial surfaces of the occipital lobes. The left occipital lobe

Key Points

- 1▶ Neurologic surgery specializes in primarily surgical management of central, peripheral, and autonomic nervous system disorders.
- 2▶ Although clinical examination is paramount, neurosurgical diagnosis and treatment are aided largely by a variety of modalities, such as MRI and intracranial pressure monitoring.
- 3▶ The common treatment goals for traumatic brain and spinal injury are aimed at preventing secondary insults of hypoxia and hypotension.
- 4▶ Aneurysmal subarachnoid hemorrhage remains one of the most morbid and intensive neurosurgical diseases. Endovascular therapy is a growing technology that allows for safer securing of ruptured aneurysms.
- 5▶ Brain tumors can arise from primary or metastatic tissues. Treatment typically involves resection, followed by radiation and/or chemotherapy, depending on the type and grade of tumor.
- 6▶ Spinal instrumentation is used for surgical stabilization of many types of spinal instability, including traumatic, infectious, oncologic, and degenerative.
- 7▶ Infection of the nervous system is a serious and prevalent medical problem. Operative management is indicated for most conditions in which there is symptomatic compression of neural structures.
- 8▶ Functional neurosurgery via device implantation is a rapidly evolving discipline that has already become the standard of care in treating medically refractory Parkinson's disease and essential tremor. A wider variety of deep brain stimulation targets will treat additional neuropsychiatric diseases.
- 9▶ Stereotactic radiosurgery is a powerful treatment option for intracranial disease, whether it is primary or adjunct. Gamma knife surgery can be used to treat tumors, vascular malformations, and cranial neuralgias.

receives and integrates data from the left half of each retina. A left occipital lesion would therefore result in an inability to see objects right of center. The temporal lobes lie below the sylvian fissures. The hippocampus, amygdala, and lower optic radiations (Meyer's loops) are important components of the temporal lobe and are involved in memory, emotion, and vision, respectively. The receptive speech area (Wernicke's area) typically is found in the area of the left posterior superior temporal lobe and inferior parietal lobe. The basal ganglia include the caudate, putamen, globus pallidus, subthalamic nucleus, substantia nigra, and nucleus accumbens. These structures are involved in the selection, activation and termination of movement, and facilitate learning of appropriate context-dependent motor behaviors.

Lying deep to the cerebral hemispheres is the diencephalon, which includes the thalamus and hypothalamus. The thalamus is a key processor and relay circuit for most motor and sensory information traveling to or from cortex. The hypothalamus regulates homeostasis via the autonomic and neuroendocrine systems.

The brain stem consists of the midbrain (mesencephalon), pons (metencephalon), and medulla (myelencephalon). Longitudinal fibers run through the brain stem, carrying motor and sensory information between the cerebral hemispheres and spinal cord. The corticospinal tract is the major motor tract, while the medial lemniscus and spinothalamic tracts are the major sensory tracts. The nuclei of cranial nerves III through XII are also located within the brain stem. These nerves relay the motor, sensory, and special sense functions of the eye, face, mouth, and throat.

The cerebellum arises from the dorsal aspect of the brain stem. It integrates somatosensory, vestibular, and motor information for coordination and timing of movement. Midline, or vermal, lesions lead to truncal ataxia. Lateral, or hemispheric, lesions lead to tremor and dyscoordination in the extremities.

The ventricular system is the cerebrospinal fluid (CSF)—containing contiguous space inside the brain, continuous with the subarachnoid space outside the brain. The paired lateral ventricles consist of temporal, occipital, and frontal horns, as well as the main body. CSF travels from each lateral ventricle through the foramina of Monroe to the third ventricle, located between the left and right thalami. CSF then drains through the cerebral aqueduct to the fourth ventricle within the brain

stem. The foramen of Magendie (midline) and paired foramina of Luschka (lateral) drain to the subarachnoid space. The approximate CSF volume in an average adult is 150 mL, and the choroid plexus produces approximately 500 mL of CSF per day.

The spinal cord starts at the bottom of the medulla and extends caudally through the spinal canal to the first lumbar vertebra, approximately. Motor tracts (efferent pathways) continue from the brain stem down via the lateral and anterior corticospinal tracts to anterior horn cells, and then exit via ventral nerve roots. Sensory information (afferent pathways) enters via dorsal nerve roots, travels cranially via the dorsal columns (proprioception and fine touch) or spinothalamic tract (pain and temperature), and into the brain stem. Paired nerves exit the spinal cord at each level. There are 31 pairs: 8 cervical, 12 thoracic, 5 lumbar, 5 sacral, and 1 coccygeal.

The dorsal and ventral nerve roots at each level fuse to form mixed motor-sensory spinal nerves and spread through the body to provide innervation to muscles and sensory organs. The C5–T1 spinal nerves intersect in the brachial plexus and divide to form the main nerve branches to the arm, including the median, ulnar, and radial nerves. The L2–S4 spinal nerves intersect in the lumbosacral plexus, and divide to form the main nerve branches to the leg, including the femoral and sciatic nerves.

The principal motor tract of the spinal cord is the corticospinal tract. It is a two-neuron path, including an upper motor neuron and a lower motor neuron. The upper motor neuron cell body is located within the motor strip of the cerebral cortex. The axon travels through the internal capsule to the brain stem, decussates at the brain stem–spinal cord junction, and travels down the contralateral corticospinal tract to the lower motor neuron in the anterior horn at the appropriate level. The lower motor neuron axon then travels via peripheral nerves to its target muscle. Damage to upper motor neurons typically results in hyperreflexia and mild atrophy. Damage to lower motor neurons results in flaccidity and significant atrophy.

The two major sensory tracts are three-neuron pathways. Fine touch and proprioceptive signals enter the spinal cord via the dorsal root ganglia and then ascend ipsilaterally via the dorsal columns. Then they synapse and decussate in the lower medulla, travel up the contralateral medial lemniscus to make a second synapse in the thalamus, and then finally ascend to the sensory cortex. Pain and temperature fibers first synapse in the dorsal horn of the spinal cord

at their entry level, decussate, and then travel up the contralateral spinothalamic tracts to the thalamus. The second synapse occurs in the thalamus, and the output axons ascend to the sensory cortex.

The aforementioned motor and sensory tracts together constitute the somatic nervous system. In addition to this system, the ANS is the other constituent of the nervous system. The ANS carries messages for homeostasis and visceral regulation from the central nervous system (CNS) to target structures such as arteries, veins, the heart, sweat glands, and the digestive tract.¹ CNS control of the ANS arises particularly from the hypothalamus and the nucleus of the tractus solitarius. The ANS is divided into the sympathetic, parasympathetic, and enteric systems. The sympathetic system drives the “fight or flight” response, using epinephrine to increase heart rate, blood pressure, blood glucose, and temperature, as well as to dilate the pupils. It arises from the thoracolumbar spinal segments. The parasympathetic system promotes the “rest and digest” state, and uses acetylcholine to maintain basal metabolic function under nonstressful conditions. Parasympathetic fibers arise from cranial nerves III, VII, IX, and X, and from the second to fourth sacral segments. The enteric nervous system controls the complex synchronization of the digestive tract, especially the pancreas, gallbladder, and small and large bowels. It can run autonomously but is regulated by the sympathetic and parasympathetic systems.

NEUROLOGIC EXAMINATION

The neurologic examination is divided into several components, and generally is done from head to toe. First, one must assess mental status. A patient may be awake, lethargic (will follow commands and answer questions, but then returns to sleep), stuporous (difficult to arouse), or comatose (no

Table 42-1

Motor scoring system

GRADE	DESCRIPTION
0	No muscle contraction
1	Visible muscle contraction without movement across the joint
2	Movement in the horizontal plane, unable to overcome gravity
3	Movement against gravity
4	Movement against some resistance
5	Normal strength

purposeful response to voice or pain). Cranial nerves may be thoroughly tested in the awake patient, but pupil reactivity, eye movement, facial symmetry, and gag are the most relevant measures when mental status is impaired. Motor testing is based on maximal effort of major muscle groups in those able to follow commands, while assessing for amplitude and symmetry of movement to deep central pain may be all that is possible for stuporous patients. Table 42-1 details scoring for motor assessment tests. Characteristic motor reactions to pain in patients with depressed mental status include withdrawal from stimulus, localization to stimulus, flexor (decorticate) posturing, extensor (decerebrate) posturing, or no reaction (in order of worsening pathology). Figure 42-1 diagrams the clinical patterns of posturing. This forms the basis of determining the Glasgow Coma Scale (GCS) motor

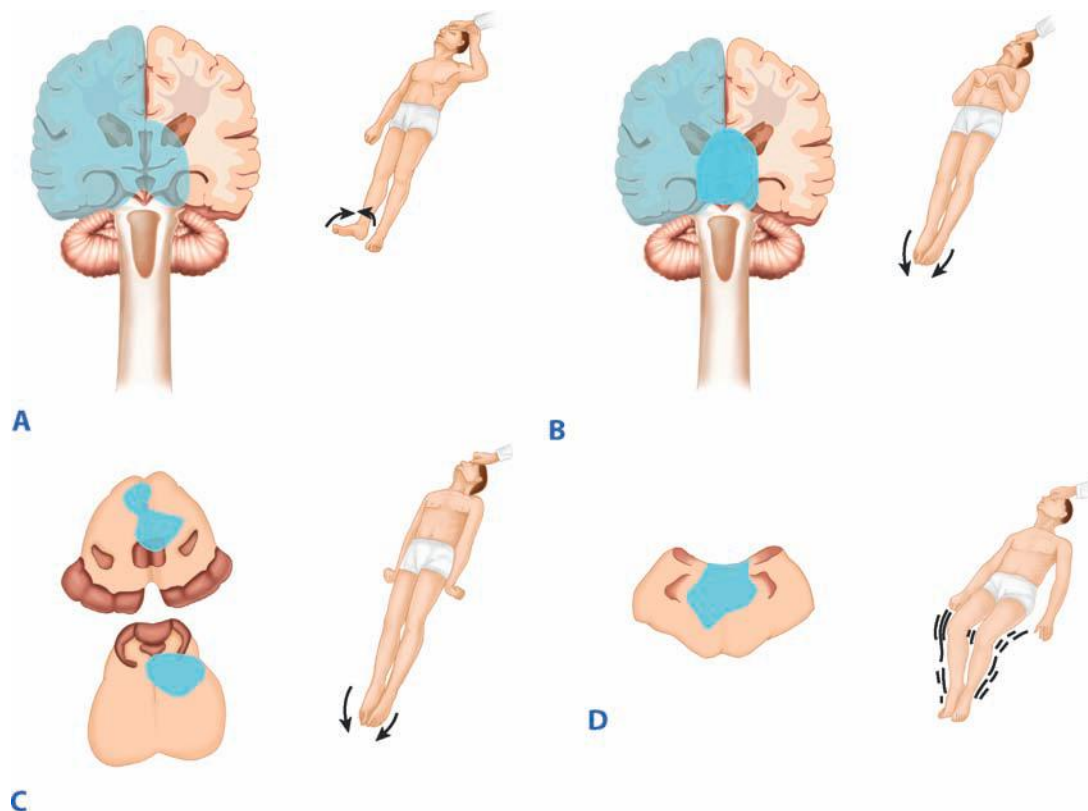


Figure 42-1. Patterns of motor responses associated with various lesions. **A.** Left hemispheric lesion with right hemiplegia and left localization. **B.** Deep cerebral/thalamic lesion with bilateral flexor posturing. **C.** Midbrain or pontine lesion with bilateral extensor posturing. **D.** Medullary lesion with general flaccidity. (Adapted with permission from Rengachary SS: *Impaired consciousness*, in Rengachary SS, Ellenbogen RG [eds]: *Principles of Neurosurgery*, 2nd ed. Edinburgh; New York: Elsevier Mosby, 2005. Copyright Elsevier.)

Table 42-2

The Glasgow Coma Scale score^a

MOTOR RESPONSE		VERBAL RESPONSE		EYE-OPENING RESPONSE	
Obeys commands	6	Oriented	5	Opens spontaneously	4
Localizes to pain	5	Confused	4	Opens to speech	3
Withdraws from pain	4	Inappropriate words	3	Opens to pain	2
Flexor posturing	3	Unintelligible sounds	2	No eye opening	1
Extensor posturing	2	No sounds	1		
No movement	1				

^aAdd the three scores to obtain the Glasgow Coma Scale (GCS) score, which can range from 3 to 15. Add "T" after the GCS if intubated and no verbal score is possible. For these patients, the GCS can range from 3T to 10T.

score, as detailed in Table 42-2. Light touch, proprioception, temperature, and pain testing may be useful in awake patients but is often impossible without good cooperation. It is critical to document sensory patterns in spinal cord injury (SCI) patients. Muscle stretch reflexes should be examined. Often comparing left to right or upper extremity to lower extremity reflexes for symmetry is the most useful for localizing a lesion. Check for ankle-jerk clonus or up-going toes (Babinski's test). Presence of either is pathologic and signifies upper motor neuron disease.

Diagnostic Studies

Plain Films. Plain X-rays of the skull may demonstrate fractures, osteolytic or osteoblastic lesions, or pneumocephaly (air in the head). The use of skull plain films has decreased given the rapid availability and significantly increased detail of head computed tomography (CT) scans. Plain films of the cervical, thoracic, and lumbar spine are used to assess for evidence of bony trauma or soft tissue swelling suggesting fracture. Spinal deformities and osteolytic or osteoblastic pathologic processes also will be apparent. The shoulder girdle usually poses problems in visualizing the cervicothoracic junction clearly.

Computed Tomography. The noncontrast CT scan of the head is an extremely useful diagnostic tool in the setting of new focal neurologic deficit, decreased mental status, or trauma. It is rapid and almost universally available in hospitals in the United States. Its sensitivity allows for the detection of acute hemorrhage. A contrast-enhanced CT scan will help show neoplastic or infectious processes. In the current era, contrast CT generally is used for those patients who cannot undergo magnetic resonance imaging (MRI) scanning due to pacemakers or metal in the orbits. Fine-slice CT scanning of the spine is helpful for defining bony anatomy and pathology, and is usually done after an abnormality is seen on plain films, or because plain films are inadequate (especially to visualize C7 and T1 vertebrae). Finally, high-speed multislice scanners, combined with timed-bolus contrast injections, allow CT angiography. A thin-slice axial scan is obtained during the passage of contrast through the cerebral arteries and reconstructed in three dimensions to assess for vascular lesions. CT angiography does not reliably detect lesions, such as cerebral aneurysms <3 mm across, but can provide detailed morphologic data of larger lesions. Newer, multislice scanner technology is approaching the resolution of conventional angiography.

Magnetic Resonance Imaging. MRI provides excellent imaging of soft tissue structures in the head and spine. It is a complex and evolving science. Several of the most clinically useful MRI sequences are worth describing. T1 sequences made before and after gadolinium administration are useful for detecting neoplastic and infectious processes. T2 sequences facilitate assessment of lesion-associated edema in the brain and neural compression in the spine by the presence or absence of bright T2 CSF signals. Diffusion-weighted images can detect ischemic stroke earlier than CT. Fine-slice time-of-flight axial images can be reformatted in three dimensions to build MRI angiograms and MRI venograms. MRI angiograms can detect stenosis of the cervical carotid arteries or intracranial aneurysms >3 mm in diameter. MRI venograms can assess the dural venous sinuses for patency or thrombosis.

Angiography. Transarterial catheter-based angiography remains the gold standard for evaluation of vascular pathology of the brain and spine. The current state of the art is biplanar imaging to reduce dye load and facilitate interventional procedures. Digital subtraction technologies minimize bony interference in the resultant images. Bilateral carotid arteries and bilateral vertebral arteries may be injected and followed through arterial, capillary, and venous phases for a complete cerebral angiogram.

Electromyography and Nerve Conduction Studies. Electromyography and nerve conduction studies (EMG/NCS) are useful for assessing the function of peripheral nerves. EMG records muscle activity in response to a proximal stimulation of the motor nerve. NCS record the velocity and amplitude of the nerve action potential. EMG/NCS typically is performed approximately 3 to 4 weeks after an acute injury, as nerves distal to the injury continue to transmit electrical impulses normally until degeneration of the distal nerve progresses.

Invasive Monitoring. The most reliable monitor, *always*, is an alert patient with a reliable neurologic examination. If a reliable neurologic examination is not possible due to the presence of brain injury, sedatives, or paralytics, or if there is active and unstable intracranial pathology, invasive monitoring is required. There are several methods of monitoring intracranial physiology. The three described below are bedside intensive care unit (ICU) procedures that allow for continuous monitoring. All three procedures involve making a small hole in the skull with a hand-held drill. They generally are placed in the right frontal

region to minimize the neurologic impact of possible complications such as hemorrhage.

External Ventricular Drain. An external ventricular drain is also known as a *ventriculostomy*. A perforated plastic catheter is inserted into the frontal horn of the lateral ventricle. An uninterrupted fluid column through a rigid tube allows transduction of intracranial pressure (ICP). CSF also can be drained to reduce ICP or sampled for laboratory studies.

Intraparenchymal Fiber-Optic Pressure Transducer. An intraparenchymal fiber-optic pressure transducer is commonly referred to as a *bolt*. A threaded post locks securely into the hole made in the skull, and holds the fiber-optic catheter in place. A bolt allows ICP monitoring only, but it is smaller and less invasive than a ventriculostomy, and may be associated with fewer complications, although the data do not clearly support this.

Brain Tissue Oxygen Sensors. The brain tissue oxygen sensor is a recent development that has already demonstrated a mortality benefit in traumatic brain injury patients.² This sensor is part of a bolt, which is screwed into the skull in the same manner as the bolt described previously, however, is engineered to hold a pressure sensor, oxygen sensor, and brain temperature sensor. The oxygen sensor catheter has an electrochemical oxygen-tension sensitive membrane. Patients with severe brain injury due to trauma or aneurysmal hemorrhage may benefit from placement of these three sensors in addition to a ventriculostomy to drain CSF for control of ICP. Such monitoring requires two twist-drill holes, which may be placed on adjacent or opposite sides of the head.

NEUROLOGIC AND NEUROSURGICAL EMERGENCIES

Raised Intracranial Pressure

ICP normally varies between 4 and 14 mmHg. Sustained ICP levels above 20 mmHg can injure the brain. The Monro-Kellie doctrine states that the cranial vault is a rigid structure, and therefore, the total volume of the contents determines ICP. The three normal contents of the cranial vault are brain tissue, blood, and CSF. The brain's contents can expand due to swelling from traumatic brain injury (TBI), stroke, or reactive edema. Blood volume can increase by extravasation to form a hematoma, or by reactive vasodilation in a hypoventilating, hypercarbic patient. CSF volume increases in the setting of hydrocephalus. Figure 42-2 demonstrates the classic CT findings of hydrocephalus. The addition of a lesion, such as a tumor or abscess, also will increase ICP. The pressure-volume curve depicted in Fig. 42-3 demonstrates a compensated region with a small $\Delta P/\Delta V$, and an uncompensated region with large $\Delta P/\Delta V$. In the compensated region, increased volume is offset by decreased volume of CSF and blood.

Increased ICP can injure the brain in several ways. Focal mass lesions cause shift and herniation. Temporal lesions push the uncus medially and compress the midbrain. This phenomenon is known as *uncal herniation*. The posterior cerebral artery (PCA) passes between the uncus and midbrain and may be occluded, leading to an occipital infarct. Masses higher up in the hemisphere can push the cingulate gyrus under the falx cerebri. This process is known as *subfalcine herniation*. The anterior cerebral artery (ACA) branches run along the



Figure 42-2. Head computed tomography scan demonstrating hydrocephalus. The third ventricle (3rd) is widened and rounded, the anterior horns of the lateral ventricles are plump, and pressure-driven flow of cerebrospinal fluid into brain parenchyma adjacent to the ventricles is seen (arrowhead). This is known as *transependymal flow of cerebrospinal fluid*.

medial surface of the cingulate gyrus and may be occluded in this case, leading to medial frontal and parietal infarcts. Diffuse increases in pressure in the cerebral hemispheres can lead to central, or transtentorial, herniation. Increased pressure in the posterior fossa can lead to upward central herniation or downward tonsillar herniation through the foramen magnum. Uncal, transtentorial, and tonsillar herniation can cause direct damage to the brain stem. Figure 42-4 diagrams patterns of herniation.

Patients with increased ICP, or intracranial hypertension, often will present with headache, nausea, vomiting, and progressive mental status decline. Cushing's triad is the classic presentation of intracranial hypertension, bradycardia, and irregular respirations. Focal neurologic deficits such as hemiparesis may be present if there is a focal mass lesion causing the problem. Patients with these symptoms should undergo an immediate head CT and rapid neurosurgical evaluation.

Initial management of intracranial hypertension includes airway protection and adequate ventilation. A bolus of mannitol up to 1 g/kg causes free water diuresis, increased serum osmolality, and extraction of water from the brain. The effect is delayed by about 20 minutes and has a transient benefit. Driving serum osmolality above 300 mOsm/L is of indeterminate benefit and can have deleterious cardiovascular side effects, such as hypovolemia that leads to hypotension and decreased brain perfusion. A ventriculostomy and/or craniectomy may be needed for definitive decompression.

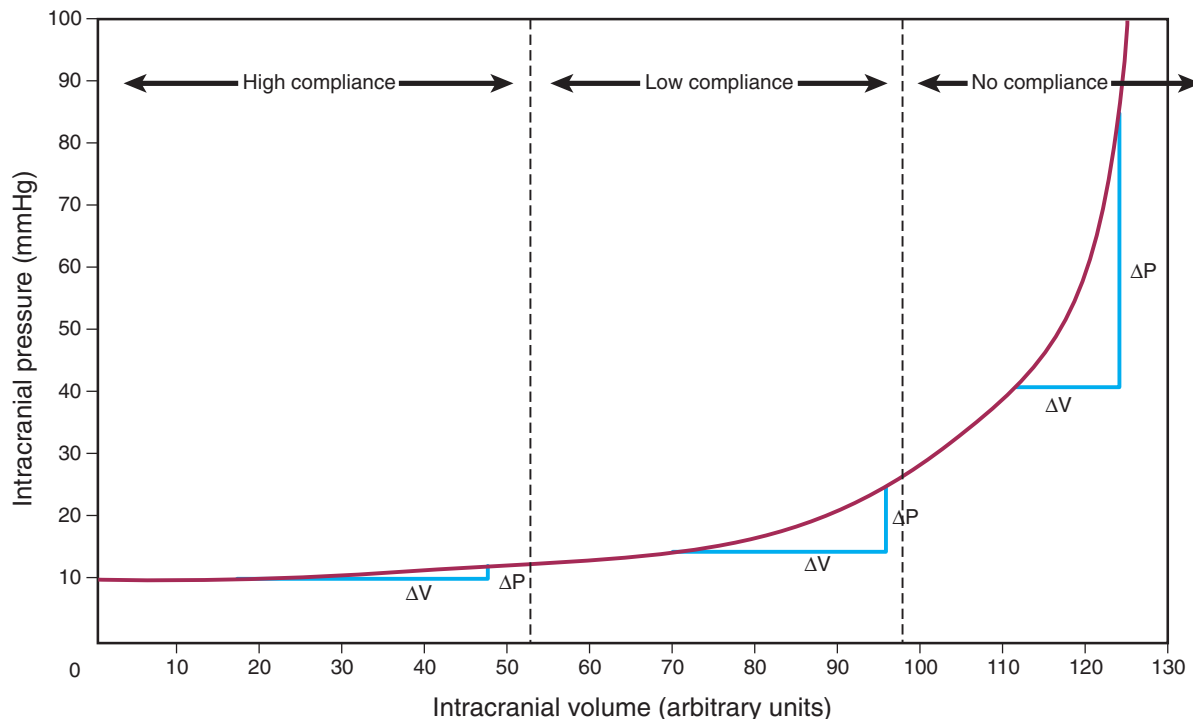


Figure 42-3. Pressure-volume curve demonstrating the effect of changing the volume of intracranial contents on intracranial pressure. Note the compensated zone, with little change of pressure with change of volume, and the uncompensated zone, with significant change of pressure with change of volume. (Adapted with permission from Morton R, Ellenbogen RG: *Intracranial consciousness*, in Ellenbogen RG et al (eds): *Principles of Neurosurgery*, 3rd ed. Philadelphia: Elsevier Saunders, 2012, p 313. Copyright Elsevier.)

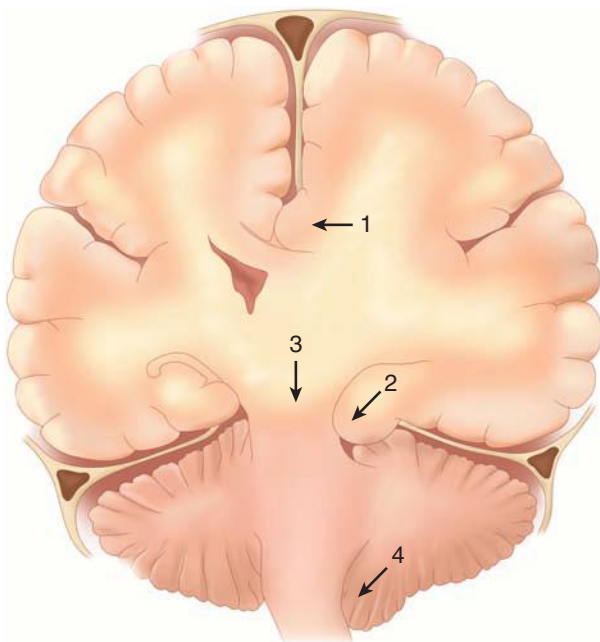


Figure 42-4. Schematic drawing of brain herniation patterns. 1. Subfalcine herniation. The cingulate gyrus shifts across midline under the falx cerebri. 2. Uncal herniation. The uncus (medial temporal lobe gyrus) shifts medially and compresses the midbrain and cerebral peduncle. 3. Central transtentorial herniation. The diencephalon and midbrain shift caudally through the tentorial incisura. 4. Tonsillar herniation. The cerebellar tonsil shifts caudally through the foramen magnum. (Reproduced with permission from Cohen DS, Quest DO: *Increased intracranial pressure, brain herniation and their control*, in Wilkins RH, Rengachary SS [eds]: *Neurosurgery*, 2nd ed. New York: McGraw Hill, 1996, p 349.)

It is critical to note that lethargic or obtunded patients often have decreased respiratory drive. This causes the partial pressure of arterial carbon dioxide ($Paco_2$) to increase, resulting in cerebral vasodilation and worsening of intracranial hypertension. This cycle causes a characteristic “crashing patient,” who rapidly loses airway protection, becomes apneic, and herniates. Emergent intubation and ventilation to reduce $Paco_2$ to roughly 35 mmHg can reverse this process.

Brain Stem Compression

The posterior fossa (brain stem and cerebellum) requires special consideration because the volume of the posterior fossa within the cranial vault is small. Posterior fossa lesions such as tumors, hemorrhage or stroke can cause mass effect that can rapidly kill the patient in two ways. Occlusion of the fourth ventricle can lead to acute obstructive hydrocephalus, raised ICP, herniation, and eventually death. This mass effect can also lead directly to brain stem compression (Fig. 42-5). Symptoms of brain stem compression include hypertension, agitation, and progressive obtundation, followed rapidly by brain death. A patient exhibiting any of these symptoms needs an emergent neurosurgical evaluation for possible ventriculostomy or suboccipital craniectomy (removal of the bone covering the cerebellum). This situation is especially critical, as expeditious decompression can lead to significant functional recovery.

Stroke

Patients presenting with acute focal neurologic deficits at a clearly defined time of onset (i.e., when the patient was last seen in a normal state of health) must be evaluated as rapidly as possible. An emergent head CT scan should be done.



Figure 42-5. Maturing cerebellar stroke seen as a hypodense area in the right cerebellar hemisphere (*arrowhead*) on head computed tomography in a patient with rapidly progressing obtundation 2 days after the initial onset of symptoms. Swelling of the infarcted tissue causes posterior fossa mass effect. The fourth ventricle is obliterated and not visible, and the brain stem is being compressed.

The study is often normal, because CT changes from ischemic stroke may take up to 24 hours to appear (Fig. 42-6). A patient with a clinical diagnosis of acute stroke <3 hours old, without hemorrhage on CT, may be a candidate for thrombolytic therapy with tissue plasminogen activator (tPA). An emergent MRI is helpful but not always diagnostically necessary.

Seizure

A seizure is defined as an uncontrolled synchronous organization of neuronal electrical activity. A new-onset seizure often signifies an irritative mass lesion in the brain, particularly in adults, in whom tumors commonly present with seizure. Patients with traumatic intracranial hemorrhage are at risk for seizure. In addition to airway and ventilatory problems, a seizing patient is also at risk for neural excitotoxicity if the activity is prolonged, such as in *status epilepticus*. Any patient with a new-onset seizure should have imaging of the brain after the seizure is controlled and the patient is resuscitated.

TRAUMA

Trauma is the leading cause of death in children and young adults; however, the incidence of death and disability from trauma has been slowly decreasing. This decline is partly attributable to increased awareness of safety devices such as seat belts and motorist helmets. Nonetheless, trauma remains a major cause of morbidity and mortality, and it can affect every major organ system in the body. The three main areas of neurosurgical focus are: traumatic brain injury (TBI), spinal cord injury (SCI), and peripheral nerve injury.

Head Trauma

Glasgow Coma Scale Score. The initial assessment of the trauma patient includes the primary survey, resuscitation, secondary survey, and definitive care. Neurosurgical evaluation begins during the primary survey with the determination of the GCS score (usually referred to simply as the *GCS*) for the patient. The GCS is determined by adding the scores of the best responses of the patient in each of three categories. The motor score ranges from 1 to 6, verbal from 1 to 5, and eyes from 1 to 4. The GCS therefore ranges from 3 to 15, as detailed in Table 42-2. Tracheal intubation or severe facial or eye swelling can impede verbal and eye responses. In these circumstances, the patient is given the score of 1 with a modifier, such as verbal “1T” where T = tube.

Scalp Injury. Blunt or penetrating trauma to the head can cause injury to the densely vascularized scalp, and significant blood loss can result. Direct pressure initially controls the bleeding, allowing close inspection of the injury. If a simple laceration is found, it should be copiously irrigated and closed primarily. If the laceration is short, a single-layer, percutaneous suture closure will suffice. If the laceration is long or has multiple arms, the patient may need debridement and closure in the operating room, with its superior lighting and wider selection of instruments and suture materials. Careful reapproximation of the galea will provide a more secure closure and better hemostasis. Blunt trauma also can cause crush injury with subsequent tissue necrosis. These wounds require debridement and consideration of advancement flaps to cover the defect.

Skull Fractures. The usual classification system for bony fractures may be applied to the skull. The fracture may be characterized by skull X-rays or head CT.³ A closed fracture is covered by intact skin. An open, or compound, fracture is associated with disrupted overlying skin. The fracture lines may be single (linear); multiple and radiating from a point (stellate); or multiple, creating fragments of bone (comminuted). Closed skull fractures do not normally require specific treatment. Open fractures require repair of the scalp and operative debridement. Indications for craniotomy include depression greater than the cranial thickness, intracranial hematoma, and frontal sinus involvement.⁴ Skull fractures generally indicate that a significant amount of force was transmitted to the head and should increase the suspicion for intracranial injury. Fractures that cross meningeal arteries can cause rupture of the underlying vessels and subsequent epidural hematoma (EDH) formation.

Depressed skull fractures may result from a focal injury of significant force. The inner and outer cortices of the skull are disrupted, and a fragment of bone is pressed in toward the brain in relation to adjacent intact skull. The fragment may overlap the edge of intact bone, or may plunge completely below the level of adjacent normal skull. The inner cortex of the bone fragments often has multiple sharp edges that can lacerate dura, brain, and vessels. Craniotomy is required to elevate the fracture, repair dural disruption, and obtain hemostasis in these cases (Fig. 42-7). However, fractures overlying dural venous sinuses require restraint. Surgical exploration can lead to life-threatening hemorrhage from the lacerated sinus.

Fractures of the skull base are common in head-injured patients, and they indicate significant impact. They are generally apparent on routine head CT, but should be evaluated with

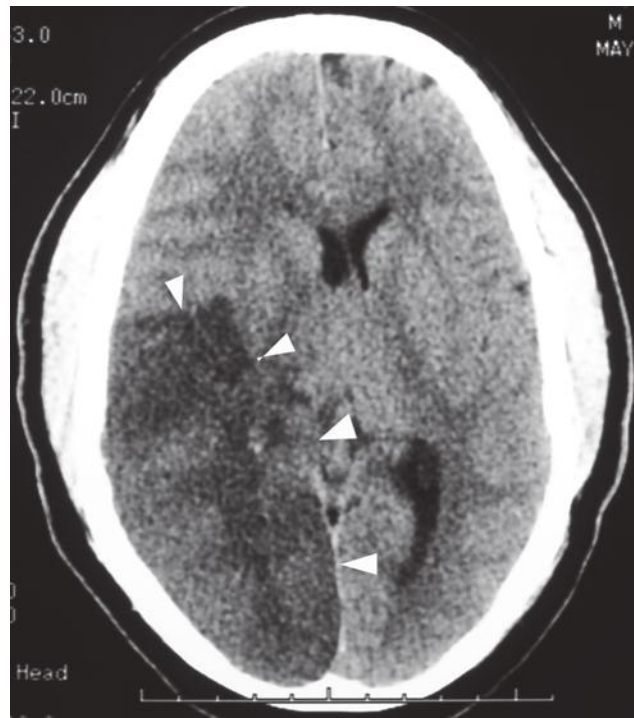
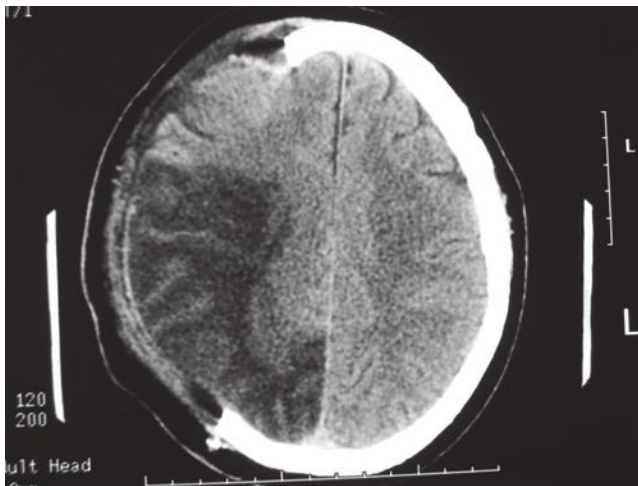
**A****B****C**

Figure 42-6. **A.** Head computed tomography scan of a patient with a 4-day-old stroke that occluded the right middle cerebral and posterior cerebral arteries. The infarcted tissue is the hypodense (*dark*) area indicated by the *arrowheads*. The patient presented with left-sided weakness and left visual field loss, but then became less responsive, prompting this head computed tomography. Note the right-to-left midline shift. **B.** Same patient status post decompressive right hemicraniectomy. Note the free expansion of swollen brain outside the normal confines of the skull. **C.** Patient with a right middle cerebral artery ischemic stroke with areas of hemorrhagic conversion, seen as hyperdense (*bright*) areas within the infarcted tissue. This patient also required hemicraniectomy for severe mass effect. Note the lack of midline shift postoperatively.

dedicated fine-slice coronal-section CT scan to document and delineate the extent of the fracture and involved structures. If asymptomatic, they require no treatment. Skull base fractures requiring intervention include those with an associated cranial nerve deficit or CSF leak. A fracture of the temporal bone, for instance, can damage the facial or vestibulocochlear nerve, resulting in vertigo, ipsilateral deafness, or facial paralysis. A communication may be formed between the subarachnoid space and the middle ear, allowing CSF drainage into the pharynx via the eustachian tube or from the ear (otorrhea). Extravasation

of blood results in ecchymosis behind the ear, known as *Battle's sign*. A fracture of the anterior skull base can result in anosmia (loss of smell from damage to the olfactory nerve), CSF drainage from the nose (rhinorrhea), or periorbital ecchymoses, known as *raccoon eyes*.

Copious clear drainage from the nose or ear makes the diagnosis of CSF leakage obvious. Often, however, the drainage may be discolored with blood or small in volume if some drains into the throat. The halo test can help differentiate. Allow a drop of the fluid to fall on an absorbent surface such as

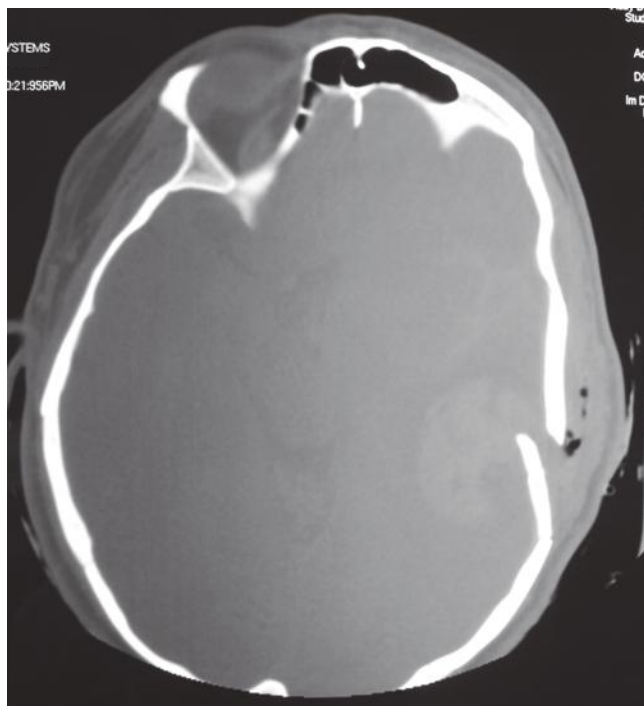
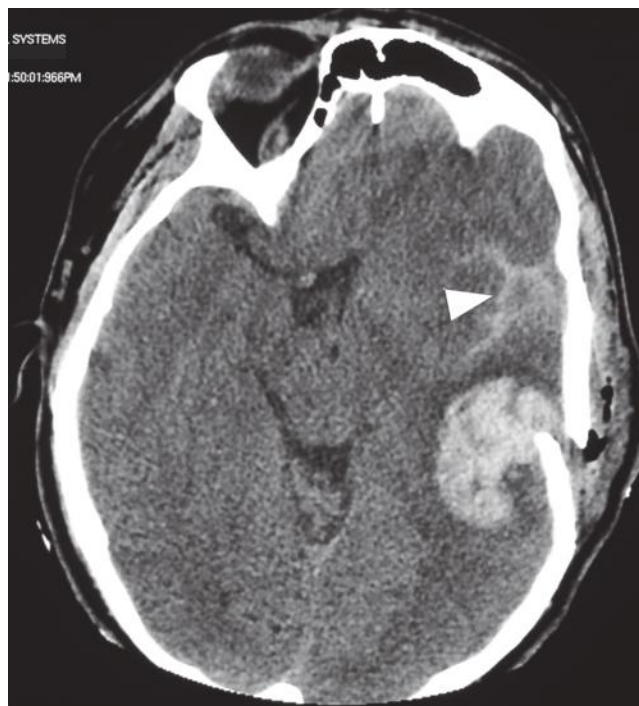
**A****B**

Figure 42-7. **A.** Bone-window axial head computed tomography (CT) of a patient who presented aphasic after being struck with the bottom of a beer bottle. CT demonstrates a depressed skull fracture in the left posterior temporoparietal area. **B.** Brain-window axial head CT demonstrating intraparenchymal hematoma caused by laceration of cortical vessels by the edge of the fractured bone. Arrowhead indicates traumatic subarachnoid hemorrhage in the sylvian fissure.

a facial tissue. If blood is mixed with CSF, the drop will form a double ring, with a darker center spot containing blood components surrounded by a light halo of CSF. If this test is indeterminate, the fluid can be sent for beta-2 transferrin testing, a carbohydrate-free isoform of transferrin exclusively found in the CSF.

Many CSF leaks will heal with elevation of the head of the bed for several days. A lumbar drain can augment this method. A lumbar drain is a catheter placed in the lumbar CSF cistern to decompress the cranial vault and allow the defect to heal by eliminating normal hydrostatic pressure. There is no proven efficacy of antibiotic coverage for preventing meningitis in patients with CSF leaks.

Traumatic cranial neuropathies generally can be managed conservatively, with documentation of the extent of impairment and signs of recovery. Patients with traumatic facial nerve palsies may benefit from a course of steroids, although their benefit is unproven. Patients with facial nerve palsy of abrupt onset, who do not respond to steroids within 48 to 72 hours, may be considered for surgical decompression of the petrous portion of the facial nerve. Patients also may present with delayed-onset facial nerve palsy. Again, steroids are used and surgery can be considered, with mixed results.

Closed Head Injury. Closed head injury (CHI) is the most common type of TBI and a significant cause of morbidity and mortality in the United States. There are two important factors that affect the outcome of CHI in general. The initial impact causes the *primary injury*, defined as the immediate injury to neurons from transmission of the force of impact. The long, delicate axons of the neurons can shear as they undergo differential acceleration or deceleration along their projecting

pathways. Prevention strategies, such as wearing helmets, remain the best means to decrease disability from primary injury. Subsequent neuronal damage due to the sequelae of trauma is referred to as *secondary injury*. Hypoxia, hypotension, hydrocephalus, intracranial hypertension, thrombosis, and intracranial hemorrhage may all be mechanisms of secondary injury. One focus of basic research in TBI, critical care medicine, and neurosurgical intervention is to decrease the effects of secondary injury.

The Brain Trauma Foundation's most recent summary of management recommendations for TBI patients was published in 2007 and is endorsed by the American Association of Neurological Surgeons, Congress of Neurological Surgeons, and the World Health Organization. The guidelines standardize the care of these patients with the hope of improving outcomes. Some of the common patterns of CHI, including concussion, contusion, and diffuse axonal injury, are discussed in Types of Closed Head Injury.⁵

Initial Assessment The initial evaluation of a trauma patient remains the same whether or not the primary surveyor suspects head injury. The first three elements of the ABCDs of resuscitation—airway, breathing, and circulation—must be assessed and stabilized. Hypoxia and hypotension are known to worsen outcome in TBI (due to secondary injury), making cardiopulmonary stabilization critical. Patients who cannot follow commands require intubation for airway protection and ventilatory control. The fourth element, assessment of “D,” for disability, is undertaken next. Motor activity, speech, and eye opening can be assessed in a few seconds and a GCS score assigned.

The following is an example of how a primary surveyor may efficiently assess disability and GCS: Approach the patient

and enter his or her field of view. Observe whether the patient is visually attentive. Clearly command: "Tell me your name." Then ask the patient to lift up two fingers on each side sequentially, and wiggle the toes. A visually or verbally unresponsive patient should be assessed for response to peripheral stimuli such as nail-bed pressure, or deep central painful stimulation, such as a firm, twisting pinch of the sensitive supraclavicular skin. Watch for eye opening and movement of the extremities, whether purposeful or reflexive. Assess the verbal response. The motor, verbal, and eye-opening scores may be correctly assigned using this rapid examination. An initial assessment of the probability of significant head injury can be made, assuming that pharmacologic and toxic elements have not obscured the examination. The surveyor must also take note of any external signs of head injury, including bleeding from the scalp, nose, or ear, or deformation of the skull or face.

Medical Management Several medical steps may be taken to minimize secondary injury and the systemic consequences of head injury. Patients with a documented CHI and evidence of intracranial hemorrhage or a depressed skull fracture should receive a 17-mg/kg phenytoin loading dose, followed by 1 week of therapeutic maintenance phenytoin, typically 300 to 400 mg/d. Phenytoin prophylaxis has been shown to decrease the incidence of early posttraumatic seizures.⁶ There is no evidence to support long-term use of prophylactic antiepileptic agents. Blood glucose levels should be closely monitored by free blood sugar checks and controlled with sliding scale insulin. Fevers also should be evaluated and controlled with antipyretics, as well as source-directed therapy when possible. Hyperglycemia and hyperthermia are toxic to injured neurons and contribute to secondary injury. Head-injured patients have an increased prevalence of peptic ulceration and GI bleeding. Peptic ulcers occurring in patients with head injury or high ICP are referred to as Cushing's ulcers. Ulcer prophylaxis should be used. Compression stockings or athrombic pumps should be used when the patient cannot be mobilized rapidly for prophylaxis of deep venous thrombosis.

Classification TBI can be classified as mild, moderate, or severe. For patients with a history of head trauma, classification is as follows: severe head injury if the GCS score is 3 to 8, moderate head injury if the GCS score is 9 to 12, and mild head injury if the GCS score is 13 to 15. Many patients present to emergency rooms and trauma bays with a history of TBI. A triage system must be used to maximize resource utilization while minimizing the chance of missing occult or progressing injuries.

TBI patients who are asymptomatic, who have only headache, dizziness, or scalp lacerations, and who did not lose consciousness, have a low risk for intracranial injury and may be discharged home without a head CT scan.^{7,8} Head-injured patients who are discharged should be sent home with reliable family or friends who can observe the patient for the first postinjury day. Printed discharge instructions, which describe monitoring for confusion, persistent nausea, weakness, or speech difficulty, should be provided to the caretaker. The patient should return to the emergency department for evaluation of such symptoms.

Patients with a history of altered consciousness, amnesia, progressive headache, skull or facial fracture, vomiting, or seizure have a moderate risk for intracranial injury and should undergo a prompt head CT. If the CT is normal, and the neurologic examination has returned to baseline (excluding amnesia

of the event), then the patient can be discharged to the care of a responsible adult, again with printed criteria for returning to the emergency room. Otherwise the patient must be admitted for a 24-hour observation period.

Patients with depressed consciousness, focal neurologic deficits, penetrating injury, depressed skull fracture, or changing neurologic examination have a high risk for intracranial injury. These patients should undergo immediate head CT and admission for observation or intervention as needed.

Types of Closed Head Injury

Concussion A concussion is defined as temporary neuronal dysfunction following nonpenetrating head trauma. The head CT is normal, and deficits resolve over minutes to hours. Definitions vary; some require transient loss of consciousness, while others include patients with any alteration of mental status. Memory difficulties, especially amnesia of the event, are very common. Concussions may be graded. One method is the Colorado grading system.⁹ Head trauma patients with confusion only are grade 1, patients with amnesia are grade 2, and patients who lose consciousness are grade 3. Studies have shown that the brain remains in a hypermetabolic state for up to a week after injury. The brain is also much more susceptible to injury from even minor head trauma in the first 1 to 2 weeks after concussion. This is known as second-impact syndrome, and patients should be informed that, even after mild head injury, they might experience memory difficulties or persistent headaches.

Contusion A *contusion* is a bruise of the brain, and occurs when the force from trauma is sufficient to cause breakdown of small vessels and extravasation of blood into the brain. The contused areas appear bright on CT scan, as seen in Fig. 42-8. The frontal,



Figure 42-8. Severe bilateral contusions in the basal aspect of the frontal lobes, caused by the brain moving over the rough, irregular skull base during sudden cranial acceleration.

occipital, and temporal poles are most often involved. The brain sustains injury as it collides with rough, bony surfaces. Contusions themselves rarely cause significant mass effect as they represent small amounts of blood in injured parenchyma rather than coherent blood clots. Edema may develop around a contusion, causing mass effect. Contusions may enlarge or progress to frank hematoma, particularly during the first 24 hours. Contusions also may occur in brain tissue opposite the site of impact. This is known as a *contre-coup injury*. These contusions result from deceleration of the brain against the skull.

Diffuse Axonal Injury Diffuse axonal injury is caused by damage to axons throughout the brain, due to rotational acceleration and then deceleration. Axons may be completely disrupted and then retract, forming axon balls. Small hemorrhages can be seen in more severe cases, especially on MRI. Hemorrhage is classically seen in the corpus callosum and the dorsolateral midbrain.

Penetrating Injury These injuries are complex and must be evaluated individually. The two main subtypes are missile (e.g., due to bullets or fragmentation devices) and nonmissile (e.g., due to knives or ice picks). Some general principles apply. If available, skull X-rays and CT scans are useful in assessing the nature of the injury. Cerebral angiography must be considered if the object passes near a major artery or dural venous sinus. Operative exploration is necessary to remove any object extending out of the cranium, as well as for debridement, irrigation, hemostasis, and definitive closure. Small objects contained within brain parenchyma are often left in place to avoid iatrogenic secondary brain injury. Antibiotics are given to decrease the chances of meningitis or abscess formation. High-velocity missile injuries (from high-powered hunting rifles or military weapons) are especially deadly, because the associated shock wave causes cavitory tissue destruction of an area that is much larger than the projectile itself. Projectiles that penetrate both hemispheres or traverse the ventricles are almost universally fatal.

Traumatic Intracranial Hematomas. The various traumatic intracranial hematomas contribute to death and disability secondary to head injury. Hematomas can expand rapidly and cause brain shift and subsequent herniation. Emergent neurosurgical evaluation and intervention often are necessary.

Epidural Hematoma EDH is the accumulation of blood between the skull and the dura. EDH usually results from arterial disruption, especially of the middle meningeal artery. The dura is adherent to bone, and some pressure is required to dissect between the two. EDH has a classic, three-stage clinical presentation that is probably seen in only 20% of cases. The patient is initially unconscious from the concussive aspect of the head trauma. The patient then awakens and has a “lucid interval,” while the hematoma subclinically expands. As the volume of the hematoma grows, the decompensated region of the pressure-volume curve is reached, ICP increases, and the patient rapidly becomes lethargic and herniates. Uncal herniation from an EDH classically causes ipsilateral third nerve palsy and contralateral hemiparesis.

On head CT the blood clot is bright, biconvex in shape (lenticular), and has a well-defined border that usually respects cranial suture lines. An EDH is typically found over the convexities but may rarely occur in the posterior fossa as well.

Open craniectomy for evacuation of the congealed clot and hemostasis generally is indicated for EDH. Patients who meet all of the following criteria may be managed conservatively: clot volume $<30 \text{ cm}^3$, maximum thickness $<1.5 \text{ cm}$, and

GCS score >8 .¹⁰ Prognosis after successful evacuation is better for EDH than subdural hematoma (SDH). EDHs are associated with lower-energy trauma with less resultant primary brain injury. Good outcomes may be seen in 85% to 90% of patients, with rapid CT scan and intervention.¹¹

Acute Subdural Hematoma An acute SDH is the result of an accumulation of blood between the arachnoid membrane and the dura. Acute SDH usually results from venous bleeding, typically from tearing of a bridging vein running from the cerebral cortex to the dural sinuses. The bridging veins are subject to stretching and tearing during acceleration/deceleration of the head, because the brain shifts in relation to the dura, which firmly adheres to the skull. Elderly and alcoholic patients are at higher risk for acute SDH formation after head trauma due to brain atrophy.

On head CT scan, the clot is bright or mixed-density, crescent-shaped (lunate), may have a less distinct border, and does not cross the midline due to the presence of the falx. Most SDHs occur over the cerebral hemispheres, but they may also occur between the hemispheres or layer over the tentorium.

Open craniotomy for evacuation of acute SDH is indicated for any of the following: thickness $>1 \text{ cm}$, midline shift $>5 \text{ mm}$, or GCS drop by two or more points from the time of injury to hospitalization. Nonoperatively managed hematomas may stabilize and eventually reabsorb, or evolve into chronic SDHs.¹² This management requires frequent neurologic examinations until the clot stabilizes based on serial head CT scans.

The prognosis for functional recovery is significantly worse for acute SDH than EDH because it is associated with greater primary injury to brain parenchyma from high-energy impacts. Prompt recognition and intervention minimizes secondary injury. The elderly patients with low admission GCS, or high postoperative ICP do poorly, with as few as 5% attaining functional recovery.¹³

Chronic Subdural Hematoma Chronic SDH is a collection of blood breakdown products that is at least 2 to 3 weeks old. Acute hematomas are bright white (hyperdense) on CT scan for approximately 3 days, after which they fade to isodensity with brain, and then to hypodensity after 2 to 3 weeks. A true chronic SDH will be nearly as dark as CSF on CT. Traces of white are often seen due to small, recurrent hemorrhages into the collection. These small bleeds may expand the collection enough to make it symptomatic. This phenomenon is referred to as an *acute-on-chronic SDH*. Figure 42-9 demonstrates the CT appearance of an acute-on-chronic SDH. Vascularized membranes form within the hematoma as it matures. These membranes may be the source of acute hemorrhage.

Chronic SDHs often occur in patients without a clear history of head trauma, as they may arise from minor head injury. Alcoholics, the elderly, and patients on anticoagulation are at higher risk for developing chronic SDH. Patients may present with headache, seizure, confusion, contralateral hemiparesis, or coma.

A chronic SDH $>1 \text{ cm}$ or any symptomatic SDH should be surgically drained. Unlike acute SDH, which consists of a thick, congealed clot, chronic SDH typically consists of a viscous fluid with the texture and dark brown color reminiscent of motor oil. A simple burr hole can effectively drain most chronic SDHs. However, the optimal treatment of chronic SDH remains controversial.¹⁴ Most authorities agree that burr hole drainage should be attempted first to obviate the risks of formal craniotomy. A single burr hole placed over the dependent edge of the



Figure 42-9. Head computed tomography scan of an elderly patient with progressing left hemiplegia and lethargy, demonstrating an acute-on-chronic subdural hematoma. History revealed that the patient sustained a fall 4 weeks before presentation. *Arrowheads* outline the hematoma. The acute component is slightly denser and is seen as the hyperdense area in the dependent portion.

collection can be made, and the space copiously irrigated until the fluid is clear. A second, more anterior burr hole can then be placed if the collection does not drain satisfactorily due to containment by membranes. The procedure is converted to open craniotomy if the SDH is too congealed for irrigation drainage, the complex of membranes prevents effective drainage, or persistent hemorrhage occurs that cannot be reached with bipolar cautery through the burr hole. The required surgical prepping and draping are always performed to allow simple conversion to craniotomy, and the scalp incision and burr holes are placed to allow easy incorporation into larger skin flaps.

There are various strategies to prevent reaccumulation of blood. Subdural or subgaleal drains may be left in place for 1 to 2 days. Mild hydration and bedrest with the head of the bed flat may encourage brain expansion. High levels of inspired oxygen may help draw nitrogen out of the cavity. Regardless of the strategy used, follow-up head CT scans are required postoperatively and approximately 1 month later to document resolution.

Intraparenchymal Hemorrhage Isolated hematomas within the brain parenchyma are most often associated with hypertensive hemorrhage or arteriovenous malformations (AVMs). Bleeding may occur in a contused area of brain. Mass effect from developing hematomas may present as a delayed neurologic deficit. Delayed traumatic intracerebral hemorrhage is most likely to occur within the first 24 hours. Patients with contusion on the initial head CT scan should be reimaged 24 hours

after the trauma to document stable pathology. Indications for craniotomy include: any clot volume $>50 \text{ cm}^3$ or a clot volume $>20 \text{ cm}^3$ with referable neurologic deterioration (GCS 6–8) and associated midline shift $>5 \text{ mm}$ or basal cistern compression.¹⁵

Vascular Injury. Trauma to the head or neck may cause damage to the carotid or vertebrobasilar systems. Generally, *dissection* refers to violation of the vessel wall intima. Blood at arterial pressures can then open a plane between the intima and media, within the media, or between the media and adventitia. The newly created space within the vessel wall is referred to as the *false lumen*. Tissue or organs supplied by dissected vessels may subsequently be injured in several ways. Expansion of the hematoma within the vessel wall can lead to narrowing of the true vessel lumen and reduction or cessation of distal blood flow. Slow-flowing or stagnant blood within the false lumen exposed to thrombogenic vessel wall elements may thrombose. Pieces of thrombus may then detach and cause distal embolic arterial occlusion. Also, the remaining partial-thickness vessel wall may rupture, damaging adjacent structures.

Traumatic dissection may occur in the carotid artery (anterior circulation) or the vertebral or basilar arteries (posterior circulation). Dissections may be extradural or intradural. Intradural dissection can present with subarachnoid hemorrhage (SAH). Traditional angiography remains the basis of diagnosis and characterization of arterial dissection. Angiographic abnormalities include stenosis of the true lumen, or “string-sign,” visible intimal flaps, and the appearance of contrast in the false lumen. Four-vessel cerebral angiography should be performed when suspicion of dissection exists.

Historically, patients with documented arterial dissection have been anticoagulated with heparin and then warfarin to prevent thromboembolic stroke. Trauma patients often have concomitant absolute or relative contraindications to anticoagulation, complicating management. Antiplatelet therapy is often implemented in lieu of full anticoagulation, however, there is no randomized clinical trial comparing the two therapies.¹⁶ Consider surgical or interventional techniques for persisting embolic disease and for vertebral dissections presenting with SAH. Surgical options include vessel ligation and bypass grafting. Interventional radiology techniques include stenting and vessel occlusion. Occlusion techniques require sufficient collateral circulation to perfuse the vascular territory previously supplied by the occluded vessel.

Carotid Dissection Carotid dissection may result from neck extension combined with lateral bending to the opposite side, or trauma from an incorrectly placed shoulder belt tightening across the neck in a motor vehicle accident. Extension or bending stretches the carotid over the bony transverse processes of the cervical vertebrae, while seat belt injuries cause direct trauma. Symptoms of cervical carotid dissection include contralateral neurologic deficit from brain ischemia, headache, and ipsilateral Horner’s syndrome from disruption of the sympathetic tracts ascending from the stellate ganglion on the surface of the carotid artery. The patient may complain of a bruit.

Traumatic vessel wall injury to the portion of the carotid artery running through the cavernous sinus may result in a carotid-cavernous fistula (CCF). This creates a high-pressure, high-flow pathophysiologic blood flow pattern. CCFs classically present with pulsatile proptosis (the globe pulses outward with arterial pulsation), retro-orbital pain, and decreased visual acuity or loss of normal eye movement (due to damage to cranial nerves

III, IV, and VI as they pass through the cavernous sinus). Symptomatic CCFs should be treated to preserve eye function. Fistulae may be closed by balloon occlusion using interventional neuro-radiology techniques. Fistulae with wide necks are difficult to treat and may require total occlusion of the parent carotid artery.

Vertebrobasilar Dissection Vertebrobasilar dissection may result from sudden rotation or flexion/extension of the neck, chiropractic manipulation, or a direct blow to the neck. Common symptoms are neck pain, headache, and brain stem stroke or SAH. The risks and benefits of aspirin therapy are unclear when a vertebral dissection extends intracranially. The theoretically increased friability of the vessel wall may increase the risk of SAH when coupled with an antiplatelet agent. Consultation of a stroke neurologist is recommended in this situation.

Brain Death. Brain death occurs when there is an absence of signs of brain stem function or motor response to deep central pain in the absence of pharmacologic or systemic medical conditions that could impair brain function.

Clinical Examination A neurologist, neurosurgeon, or intensivist generally performs the clinical brain death examination. Two examinations consistent with brain death 12 hours apart, or one examination consistent with brain death followed by a consistent confirmatory study generally is sufficient to declare brain death (see below). Hospital regulations and local laws regarding documentation should be followed closely.

Establish the absence of complicating conditions before beginning the examination. The patient must be normotensive, eutermic, and oxygenating well. The patient may not be under the effects of any sedating or paralytic drugs.

Documentation of no brain stem function requires the following: nonreactive pupils; lack of corneal blink, oculocephalic (doll's eyes), oculovestibular (cold calorics) reflexes; and loss of drive to breathe (apnea test). The apnea test demonstrates no spontaneous breathing even when $Paco_2$ is allowed to rise above 60 mmHg.

Deep central painful stimuli are provided by bilateral forceful twisting pinch of the supraclavicular skin and pressure to the medial canthal notch. Pathologic responses such as flexor or extensor posturing are *not* compatible with brain death. Spinal reflexes to peripheral pain, such as triple flexion of the lower extremities, are compatible with brain death.

Confirmatory Studies Confirmatory studies are performed after a documented clinical examination consistent with brain death. A study consistent with brain death may obviate the need to wait 12 hours for a second examination. This is especially important when the patient is a potential organ donor, as brain-dead patients often have progressive hemodynamic instability. Lack of cerebral blood flow consistent with brain death may be documented by cerebral angiography or technetium radionuclide study. A "to-and-fro" pattern on transcranial Doppler ultrasonography indicates no net forward flow through the cerebral vasculature, consistent with brain death. An electroencephalogram (EEG) documenting electrical silence has been used, but generally is not favored because there is often significant artifact which impairs interpretation.

Spine Trauma

The spine is a complex biomechanical structure. The spine provides structural support for the body as the principal component of the axial skeleton, while protecting the spinal cord and nerve roots. Trauma may fracture bones or cause ligamentous

disruption. Often, bone and ligament damage occur together. Damage to these elements reduces the strength of the spine and may cause instability, which compromises both supportive and protective functions. Spine trauma may occur with or without neurologic injury.

Neurologic injury from spine trauma is classified as either incomplete or complete. If there is some residual motor or sensory neurologic function below the level of the lesion, as assessed by clinical examination, the injury is defined as incomplete.¹⁷ A patient with complete neurologic dysfunction persisting 24 hours after injury has a very low probability of return of function in the involved area.

Neurologic injury from spine trauma may occur immediately or in delayed fashion. Immediate neurologic injury may be due to direct damage to the spinal cord or nerve roots from penetrating injuries, especially from stab wounds or gunshots. Blunt trauma may transfer sufficient force to the spine to cause acute disruption of bone and ligament, leading to subluxation, which is a shift of one vertebral element in relation to the adjacent level. Subluxation decreases the size of the spinal canal and neural foramina and causes compression of the cord or roots. Such neural impingement can also result from retropulsion of bone fragments into the canal during a fracture. Transection, crush injury, and cord compression impairing perfusion are mechanisms leading to SCI. Delayed neurologic injury may occur during transportation, examination of an improperly immobilized patient, or during a hypotensive episode.

The Mechanics of Spine Trauma. Trauma causes a wide variety of injury patterns in the spine due to its biomechanical complexity. A mechanistic approach facilitates an understanding of the patterns of injury, as there are only a few types of forces that can be applied to the spine. Although these forces are discussed individually, they often occur in combination. Several of the most common injury patterns are then presented to illustrate the clinical results of these forces applied at pathologically high levels.

Flexion/Extension Bending the head and body forward into a fetal position flexes the spine. Flexion loads the spine anteriorly (the vertebral bodies) and distracts the spine posteriorly (the spinous process and interspinous ligaments). High flexion forces occur during front-end motor vehicle collisions, and backward falls when the head strikes first. Arching the neck and back extends the spine. Extension loads the spine posteriorly and distracts the spine anteriorly. High extension forces occur during rear-end motor vehicle collisions (especially if there is no headrest), frontward falls when the head strikes first, or diving into shallow water.

Compression/Distraction Force applied along the spinal axis (axial loading) compresses the spine. Compression loads the spine anteriorly and posteriorly. High compression forces occur when a falling object strikes the head or shoulders, or when landing on the feet, buttocks, or head after a fall from height. A pulling force in line with the spinal axis distracts the spine. Distraction unloads the spine anteriorly and posteriorly. Distraction forces occur during a hanging, when the chin or occiput strikes an object first during a fall, or when a passenger submarines under a loose seat belt during a front-end motor vehicle collision.

Rotation Force applied tangential to the spinal axis rotates the spine. Rotation depends on the range of motion of intervertebral facet joints. High rotational forces occur during off-center impacts to the body or head or during glancing automobile accidents.

Patterns of Injury. Certain patterns of injury resulting from combinations of the previously mentioned forces occur commonly and should be recognized during plain film imaging of the spine. Always completely evaluate the spine. A patient with a spine injury at one level has a significant risk for additional injuries at other levels.

Cervical The cervical spine is more mobile than the thoracolumbar spine. Stability comes primarily from the multiple ligamentous connections of adjacent vertebral levels. Disruption of the cervical ligaments can lead to instability in the absence of fracture. The mass of the head transmits significant forces to the cervical spine during abrupt acceleration or deceleration, increasing risk for injury.

Jefferson Fracture A Jefferson fracture is a bursting fracture of the ring of C1 (the atlas) due to compression forces. There are usually two or more fractures through the ring of C1. The open-mouth odontoid view may show lateral dislocation of the lateral masses of C1. The rule of Spence states that 7 mm or greater combined dislocation indicates disruption of the transverse ligament. The transverse ligament stabilizes C1 with respect to C2. Jefferson fractures dislocated <7 mm usually are treated with a rigid collar, while those dislocated 7 mm or greater usually are treated with a halo vest. Surgical intervention is not indicated.

Odontoid Fractures The odontoid process, or dens, is the large ellipse of bone arising anteriorly from C2 (the axis) and projecting up through the ring of C1 (the atlas). Several strong ligaments connect the dens to C1 and to the base of the skull. Odontoid fractures usually result from flexion forces. Odontoid fractures are classified as type I, II, or III. A type I fracture involves the tip only. A type II fracture passes through the base of the odontoid process. A type III fracture passes through the body of C2. Types II and III are considered unstable and should be externally immobilized or fused surgically. Surgery often is undertaken for widely displaced fractures (poor chance of fusing) and for those that fail external immobilization. Type I fractures usually fuse with external immobilization only.

Hangman's Fracture Traditionally considered a hyperextension/distraction injury from placement of the noose under the angle of the jaw, hangman's fractures also may occur with hyperextension/compression, as with diving accidents, or hyperflexion. The injury is defined by bilateral C2 pars interarticularis fractures. The pars interarticularis is the bone between superior and inferior facet joints. Thus, the posterior bony connection between C1 and C3 is lost. Hangman's fractures heal well with external immobilization. Surgery is indicated if there is spinal cord compression or after failure of external immobilization.

Jumped Facets—Hyperflexion Injury The facet joints of the cervical spine slope forward. In a hyperflexion injury, the superior facet can "jump" over the inferior facet of the level above if the joint capsule is torn. Hyperflexion/rotation can cause a unilateral jumped facet, whereas hyperflexion/distraction leads to bilateral jumped facets. Patients with unilateral injury usually are neurologically intact. Those with bilateral injury, however, typically suffer from spinal cord damage, since the anteroposterior diameter of the spinal canal is compromised by bilateral injury, leading to spinal cord compression (Fig. 42-10).

Thoracolumbar The thoracic spine is stabilized significantly by the rib cage. The lumbar spine has comparatively large vertebrae. Thus, the thoracolumbar spine has a higher threshold for injury than the cervical spine. A three-column model is useful for categorizing thoracolumbar injuries.¹⁸ The anterior longitudinal ligament and the anterior half of the vertebral body constitute the anterior column. The posterior half of the vertebral body and the posterior longitudinal ligament constitute the middle column. The pedicles, facet joints, laminae, spinous processes, and interspinous ligaments constitute the posterior column.

Compression Fracture Compression fracture is a compression/flexion injury causing failure of the anterior column only. It is stable and not associated with neurologic deficit, although the patient may still have significant pain (Fig. 42-11).

Burst Fracture Burst fracture is a pure axial compression injury causing failure of the anterior and middle columns. It is unstable, and perhaps half of patients have neurologic deficit due to compression of the cord or cauda equina from bone fragments retropulsed into the spinal canal.

Chance Fracture Chance fracture is a flexion-distraction injury causing failure of the middle and posterior columns, sometimes with anterior wedging. Typical injury is from a lap seat-belt hyperflexion with associated abdominal injury. It often is unstable and associated with neurologic deficit.

Fracture-Dislocation Fracture-dislocation is failure of the anterior, middle, and posterior columns caused by flexion/distraction, shear, or compression forces. Neurologic deficit can result from retropulsion of middle column bone fragments into the spinal canal, or from subluxation causing decreased canal diameter (Fig. 42-12).

Initial Assessment and Management. The possibility of a spine injury must be considered in all trauma patients. A patient with no symptoms referable to neurologic injury, a normal neurologic examination, no neck or back pain, and a known mechanism of injury unlikely to cause spine injury is at minimal risk for significant injury to the spine. Victims of moderate or severe trauma, especially those with injuries to other organ systems, usually fail to meet these criteria or cannot be assessed adequately. The latter often is due to impaired sensorium or significant pain. Because of the potentially catastrophic consequences of missing occult spine instability in a neurologically intact patient, a high level of clinical suspicion should govern patient care until completion of clinical and radiographic evaluation.

The trauma patient should be kept on a hard flat board with straps and pads used for immobilization. A hard cervical collar is kept in place. These steps minimize forces transferred through the spine, and therefore decrease the chance of causing dislocation, subluxation, or neural compression during transport to the trauma bay. The patient is then moved from the board to a flat stretcher. The primary survey and resuscitation are completed. Physical examination and initial X-rays follow.

For the examination, approach the patient as described in the section on Neurologic Examination earlier in this chapter. Evaluation for spine or SCI is easier and more informative in awake patients. If the patient is awake, ask if he or she recalls details of the nature of the trauma, and if there

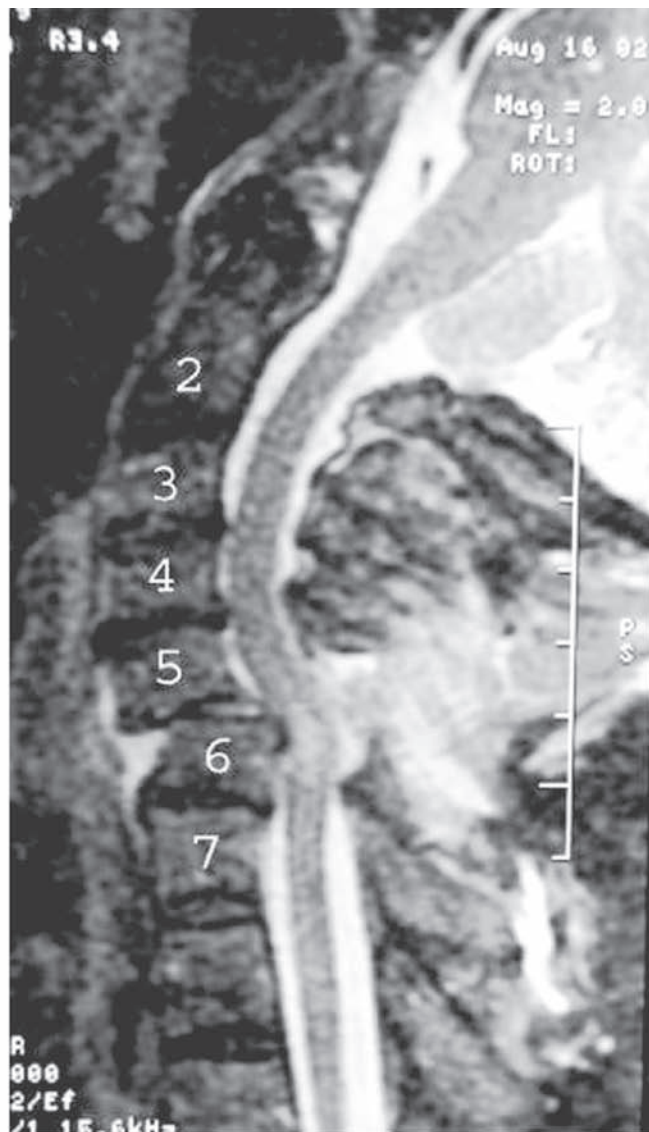
**A****C****D****B**

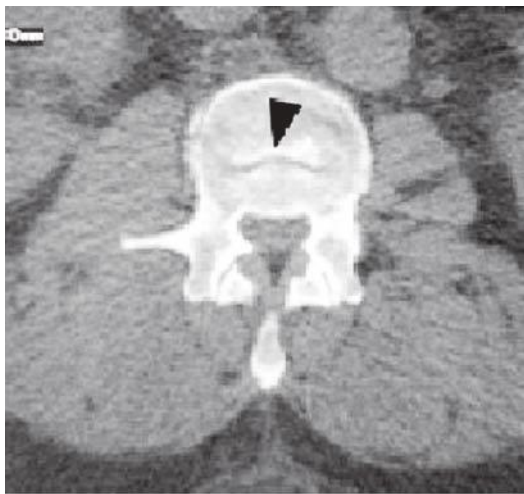
Figure 42-10. **A.** Lateral cervical spine X-ray of an elderly woman who struck her head during a backward fall. *Arrowhead* points to jumped facets at C5–C6. Note the anterior displacement of the C5 body with respect to the C6 body. **B.** Sagittal T2-weighted magnetic resonance imaging of the same patient, revealing compromise of the spinal canal and compression of the cord. Note the bright signal within the cord at the level of compression, indicating spinal cord injury. **C.** Lateral cervical spine X-ray of same patient after application of cervical traction and manual reduction. Note restoration of normal alignment. **D.** Lateral cervical spine X-ray after posterior cervical fusion to restabilize the C5–C6 segment of the spine.

was loss of consciousness, numbness, or inability to move any or all limbs. Assess motor function by response to commands or pain, as appropriate. Assess pinprick, light touch, and joint position, if possible. Determining the anatomically lowest level of intact sensation can pinpoint the level of the

lesion along the spine. Testing sensation in an ascending fashion will allow the patient to better discern the true stimulus as opposed to determine when it is extinguished. Document muscle stretch reflexes, lower sacral reflexes (i.e., anal wink and bulbocavernosus), and rectal tone.



A



B

Figure 42-11. **A.** Lateral lumbar spine X-ray showing a compression fracture of L2. *Arrowhead* points to anterior wedge deformity. Note the posterior wall of the vertebral body has retained normal height and alignment. **B.** Axial computed tomography scan through the same fracture. *Arrowhead* demonstrates a transverse discontinuity in the superior endplate of the L2 body.

American Spinal Injury Association Classification The American Spinal Injury Association provides a method of classifying patients with spine injuries. The classification indicates completeness and level of the injury and the associated deficit. A form similar to that shown in Fig. 42-13 should be available in the trauma bay and completed for any spine injury patient. The



Figure 42-12. Sagittal reconstruction of an axial fine-slice computed tomography scan through the lumbar spine demonstrating a severe fracture-dislocation through the body of L2.

association also has worked to develop recommendations and guidelines to standardize the care of SCI patients in an effort to improve the quality of care.

Neurologic Syndromes. Penetrating, compressive, or ischemic cord injury can lead to several characteristic presentations based on the anatomy of injury. The neurologic deficits may be deduced from the anatomy of the long sensory and motor tracts and understanding of their decussations (Fig. 42-14). Four patterns are discussed. First, injury to the entire cord at a given level results in anatomic or functional cord transection with total loss of motor and sensory function below the level of the lesion. The typical mechanism is severe traumatic vertebral subluxation reducing spinal canal diameter and crushing the cord. Second, injury to half the cord at a given level results in Brown-Séquard syndrome, with loss of motor control and proprioception ipsilaterally and loss of nociception and thermoception contralaterally. The typical mechanism is a stab or gunshot wound. Third, injury to the interior gray matter of the cord in the cervical spine results in a central cord syndrome, with upper extremity worse than lower extremity weakness and various degrees of numbness. The typical mechanism is transient compression of the cervical cord by the ligamentum flavum buckling during traumatic neck hyperextension. This syndrome occurs in patients with preexisting cervical stenosis. Fourth, injury to the ventral half of the cord results in the anterior cord syndrome, with paralysis and loss of nociception and thermoception bilaterally. The typical mechanism is an acute disc herniation or ischemia from anterior spinal artery occlusion.

Studies. Anteroposterior and lateral plain films provide a rapid survey of the bony spine. Plain films detect fractures

ASIA IMPAIRMENT SCALE

☐ **A = Complete:** No motor or sensory function is preserved in the sacral segments S4-S5.

☐ **B = Incomplete:** Sensory but not motor function is preserved below the neurological level and includes the sacral segments S4-S5.

☐ **C = Incomplete:** Motor function is preserved below the neurological level, and more than half of key muscles below the neurological level have a muscle grade less than 3.

☐ **D = Incomplete:** Motor function is preserved below the neurological level, and at least half of key muscles below the neurological level have a muscle grade of 3 or more.

☐ **E = Normal:** motor and sensory function are normal

CLINICAL SYNDROMES

☐ Central Cord

☐ Brown-Sequard

☐ Anterior Cord

☐ Conus Medullaris

☐ Cauda Equina

ASIA STANDARD NEUROLOGICAL CLASSIFICATION OF SPINAL CORD INJURY

MOTOR KEY MUSCLES

	R	L
C2		
C3		
C4		
C5		
C6		
C7		
C8		
T1		
T2		
T3		
T4		
T5		
T6		
T7		
T8		
T9		
T10		
T11		
T12		
L1		
L2		
L3		
L4		
L5		
S1		
S2		
S3		
S4-S5		

0 = total paralysis
1 = palpable or visible contraction
2 = active movement, gravity eliminated
3 = active movement, against gravity
4 = active movement, against some resistance
5 = active movement, against full resistance
NT = not testable

Elbow flexors
Wrist extensors
Elbow extensors
Finger flexors (distal phalanx of middle finger)
Finger abductors (little finger)

Hip flexors
Knee extensors
Ankle dorsiflexors
Long toe extensors
Ankle plantar flexors

☐ Voluntary anal contraction (Yes/No)

SENSORY KEY SENSORY POINTS

	R	L
C2		
C3		
C4		
C5		
C6		
C7		
C8		
T1		
T2		
T3		
T4		
T5		
T6		
T7		
T8		
T9		
T10		
T11		
T12		
L1		
L2		
L3		
L4		
L5		
S1		
S2		
S3		
S4-S5		

0 = absent
1 = impaired
2 = normal
NT = not testable

Any anal sensation (Yes/No)

TOTALS ☐ + ☐ = ☐ **MOTOR SCORE**

(MAXIMUM) (50) (50) (100)

TOTALS ☐ + ☐ = ☐ **PIN PRICK SCORE**

(MAXIMUM) (56) (56) (56) (56)

TOTALS ☐ + ☐ = ☐ **LIGHT TOUCH SCORE**

(MAXIMUM) (56) (56) (56) (56)

NEUROLOGICAL LEVEL ☐ R ☐ L

COMPLETE OR INCOMPLETE? ☐ Incomplete = Any sensory or motor function in S4-S5

ASIA IMPAIRMENT SCALE ☐

ZONE OF PARTIAL PRESERVATION ☐ Caudal extent of partially innervated segments

SENSORY MOTOR ☐ R ☐ L

This form may be copied freely but should not be altered without permission from the American Spinal Injury Association. 2000 Rev.

Figure 42-13. The American Spinal Injury Association system for categorizing spinal cord injury patients according to level and degree of neurologic deficit.

and dislocations well. Adequate visualization of the lower cervical and upper thoracic spine often is impossible because of the shoulder girdle. Complete plain film imaging of the cervical spine includes an open-mouth view to assess the odontoid process and the lateral masses of C1. Fine-slice CT scan with sagittal and coronal reconstructions provides good detail of bony anatomy and is good for characterizing fractures seen on plain films, as well as visualizing C7–T1 when not well seen on plain films. MRI provides the best soft tissue imaging. Canal compromise from subluxation, acute disc herniations, or ligamentous disruption is clearly

seen. MRI also may detect EDHs or damage to the spinal cord itself, including contusions or areas of ischemia.

Definitive Management

Spinal-Dose Steroids The National Acute Spinal Cord Injury studies (NASCIS I and II) provide the basis for the common practice of administering high-dose steroids to patients with acute SCI. A 30-mg/kg IV bolus of methylprednisolone is given over 15 minutes, followed by a 5.4-mg/kg per hour infusion begun 45 minutes later. The infusion is continued for 23 hours if the bolus is given within 3 hours of injury, or for 47 hours if

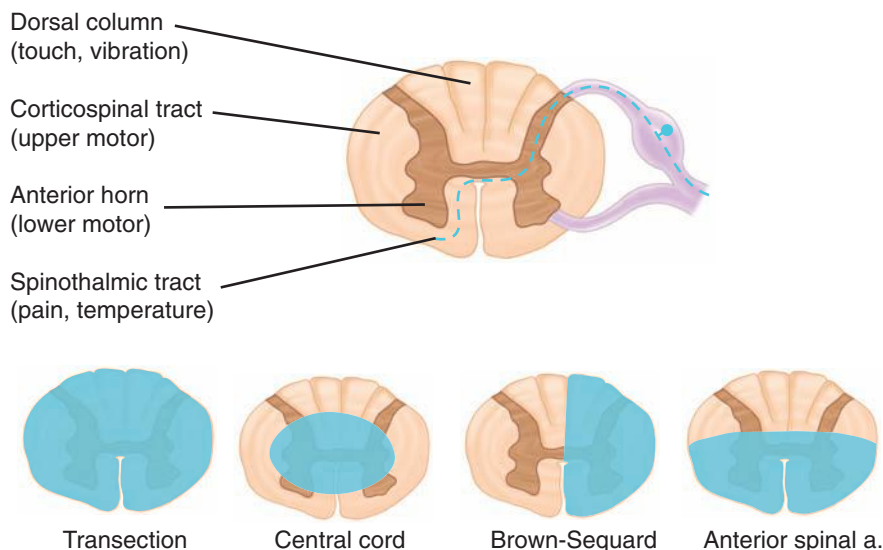


Figure 42-14. Spinal cord injury patterns. a. = artery. (Adapted with permission from Hoff J, Boland M: *Neurosurgery*, in Schwartz SI, et al (eds): *Principles of Surgery*, 7th ed., New York: McGraw-Hill, 1999, p 1837. Copyright © The McGraw-Hill Companies, Inc.)

the bolus is given within 8 hours of injury. The papers indicate greater motor and sensory recovery at 6 weeks, 6 months, and 1 year after acute SCI in patients who received methylprednisolone.^{19,20} However, the NASCIS trial data have been extensively criticized, as many argue that the selection criteria and study design were flawed, making the results ambiguous. Patients who receive such a large corticosteroid dose have increased rates of medical and ICU complications, such as pneumonias, which have a deleterious effect on outcome. Thus, clear consensus on the use of spinal-dose steroids does not exist.²¹ A decision to use or not use spinal-dose steroids may be dictated by local or regional practice patterns, especially given the legal liability issues surrounding SCI. Patients with gunshot or nerve root (cauda equina) injuries, or those who are pregnant, <14 years old, or on chronic steroids were excluded from the NASCIS studies and should not receive spinal-dose steroids. In addition to steroids, hypothermia for SCI has also received attention. There is even less evidence supporting the use of this treatment, and thus, it is not currently recommended.²²

Orthotic Devices Rigid external orthotic devices can stabilize the spine by decreasing range of motion and minimizing stress transmitted through the spine. Commonly used rigid cervical orthoses include Philadelphia and Miami-J collars. Cervical collars are inadequate for C1, C2, or cervicothoracic instability. Cervicothoracic orthoses brace the upper thorax and the neck, improving stabilization over the cervicothoracic region. Minerva braces improve high cervical stabilization by bracing from the upper thorax to the chin and occiput. Halo-vest assemblies provide the most external cervical stabilization. Four pins are driven into the skull to lock the halo ring in position. Four posts arising from a tight-fitting rigid plastic vest immobilize the halo ring. Lumbar stabilization may be provided by thoracolumbosacral orthoses. A variety of companies manufacture lines of spinal orthotics. A physician familiar with the technique should fit a halo-vest. Assistance from a trained orthotics technician improves fitting and adjustment of the other devices.

Surgery Neurosurgical intervention has two goals. First is the decompression of the spinal cord or nerve roots in patients with incomplete neurologic deficits. These patients should be decompressed expeditiously, especially if there is evidence of neurologic deterioration over time. Second is the stabilization of injuries judged too unstable to heal with external immobilization only. Spine trauma patients with complete neurologic deficit, without any signs of recovery, or those without any neurologic deficits who have bony or ligamentous injury requiring open fixation, may be medically stabilized before undergoing surgery. Surgical stabilization may be indicated for some injuries that would eventually heal with conservative treatment. It also can allow early mobilization, aggressive nursing care, and physical therapy. Solid surgical stabilization may also allow a patient to be managed with a rigid cervical collar who would otherwise require halo-vest immobilization.

Continued Care. Regional SCI centers with nurses, respiratory therapists, pulmonologists, physical therapists, physiatrists, and neurosurgeons specifically trained in caring for these patients may improve outcomes. Frequently encountered ICU issues include hypotension and aspiration pneumonia. Chronically, prevention and treatment of deep venous thrombosis, autonomic hyperreflexia, and decubitus ulcer formation are important. Many patients with cervical or high thoracic cord injuries require prolonged ventilatory support until the chest

wall becomes stiff enough to provide resistance for diaphragmatic breathing. Patients with high cervical cord injuries (C4 or above) will often require permanent ventilatory support. Patients should be transferred to SCI rehabilitation centers after stabilization of medical and surgical issues.

Peripheral Nerve Trauma

The peripheral nervous system extends throughout the body and is subject to injury from a wide variety of trauma. Peripheral nerves transmit motor and sensory information from the CNS to the body. An individual nerve may have pure motor, pure sensory, or mixed motor and sensory functions. The key information-carrying structure of the nerve is the axon. The axon transmits information from the neuronal cell body and may measure from <1 mm to >1 m in length. Axons that travel a significant distance are often covered with myelin, which is a lipid-rich, electrically insulating sheath formed by Schwann cells. Myelinated axons transmit signals much more rapidly than unmyelinated axons because the voltage shifts and currents that define action potentials effectively jump from gap to gap over the insulated lengths of the axon.

Axons, whether myelinated or unmyelinated, travel through a collagenous connective tissue known as *endoneurium*. Groups of axons and their endoneurium form bundles known as *fascicles*. Fascicles run through a tubular collagenous tissue known as *perineurium*. Groups of fascicles are suspended in *mesoneurium*. Fascicles and their mesoneurium run through another tubular collagenous tissue known as *epineurium*. The epineurium and its contents form the nerve.

There are four major mechanisms of injury to peripheral nerves. Nerves may be lacerated, stretched, compressed, or contused. Knives, passing bullets, or jagged bone fractures may lacerate nerves. Adjacent expanding hematomas or dislocated fractures may stretch nerves. Expanding hematomas, external orthoses such as casts or braces, or blunt trauma over a superficial nerve may compress or crush nerves. Shock waves from high-velocity bullets may contuse nerves. These mechanisms of injury cause damage to the various anatomic components of the nerve. The patterns of damage are categorized in Types of Injury section.

Certain nerve segments are particularly vulnerable to injury. The following four characteristics make a nerve segment more vulnerable: proximity to a joint, superficial course, passage through a confined space, and being fixed in position.

Types of Injury. The traditional classification system for peripheral nerve injury is the Seddon classification. Seddon described three injury patterns as defined in the Neurapraxia, Axonotmesis, and Neurotmesis sections. The Seddon classification provides a simple, anatomically based approach to peripheral nerve injury.²³

Neurapraxia Neurapraxia is defined as the temporary failure of nerve function without physical axonal disruption. Axon degeneration does not occur. Return of normal axonal function occurs over hours to months, often in the 2- to 4-week range.

Axonotmesis Axonotmesis is the disruption of axons and myelin. The surrounding connective tissues, including endoneurium, are intact. The axons degenerate proximally and distally from the area of injury. Distal degeneration is known as *Wallerian degeneration*. Axon regeneration within the connective tissue pathways can occur, leading to restoration of function. Axons regenerate at a rate of 1 mm per day. Significant functional recovery may occur for up to 18 months. Scarring at the site of injury from connective tissue reaction can form a neuroma and interfere with regeneration.

Neurotmesis Neurotmesis is the disruption of axons and endoneurial tubes. Peripheral collagenous components, such as the epineurium, may or may not be intact. Proximal and distal axonal degeneration occurs. The likelihood of effective axonal regeneration across the site of injury depends on the extent of neuroma formation and on the degree of persisting anatomic alignment of the connective tissue structures. For instance, an injury may damage axons, myelin, and endoneurium, but leave perineurium intact. In this case, the fascicle sheath is intact, and appropriate axonal regeneration is more likely to occur than if the sheath is interrupted.

Management of Peripheral Nerve Injury. The sensory and motor deficits should be accurately documented. Deficits are usually immediate. Progressive deficit suggests a process such as an expanding hematoma and may warrant early surgical exploration. Clean, sharp injuries may also benefit from early exploration and reanastomosis. Most other peripheral nerve injuries should be observed. EMG/NCS studies should be done 3- to weeks postinjury if deficits persist. Axon segments distal to the site of injury will conduct action potentials normally until Wallerian degeneration occurs, rendering EMG/NCS before 3 weeks uninformative. Continued observation is indicated if function improves. Surgical exploration of the nerve may be undertaken if no functional improvement occurs over 3 months. If intraoperative electrical testing reveals conduction across the injury, continue observation. In the absence of conduction, the injured segment should be resected and end-to-end primary anastomosis attempted. However, anastomoses under tension will not heal. A nerve graft may be needed to bridge the gap between the proximal and distal nerve ends. The sural nerve often is harvested, as it carries only sensory fibers and leaves a minor deficit when resected. The connective tissue structures of the nerve graft may provide a pathway for effective axonal regrowth across the injury.

Patterns of Injury

Brachial Plexus The brachial plexus may be injured in a variety of ways. Parturition or a motorcycle accident can lead to plexus injury due to dislocation of the glenohumeral joint. Attempting to arrest a fall with one's hands can lead to a stretch injury of the plexus due to abrupt movement of the shoulder girdle. An apical lung (Pancoast) tumor can cause compression injury to the plexus. There are many patterns of neurologic deficits possible with injury to the various components of the brachial plexus, and understanding them all would require extensive neuroanatomic discussion. Two well-known eponymous syndromes are Erb's palsy and Klumpke's palsy. Injury high in the plexus to the C5 and C6 roots resulting from glenohumeral dislocation causes Erb's palsy with the characteristic "bellhop's tip" position. The arm hangs at the side, internally rotated. Hand movements are not affected. Injury low in the plexus, to the C8 and T1 roots, resulting from stretch or compression injury, causes Klumpke's palsy with the characteristic "claw hand" deformity. There is weakness of the intrinsic hand muscles, similar to that seen with ulnar nerve injury.

Radial Nerve The radial nerve courses through the axilla, then laterally and posteriorly in the spiral groove of the humerus. Improper crutch use can cause damage to the axillary portion. The section of the nerve traversing the spiral groove can be damaged by humerus fractures or pressure from improper positioning during sleep. This classically occurs when the patient is intoxicated and is called "Saturday night palsy." The key finding is wrist drop (i.e., weakness of hand and finger extensors). Axillary (proximal) injury causes triceps weakness in addition to wrist drop.

Common Peroneal Neuropathy The common peroneal nerve forms the lateral half of the sciatic nerve (the medial half being the tibial nerve). It receives contributions from L4, L5, S1, and S2. It emerges as a separate nerve in the popliteal fossa and laterally wraps around the fibular neck, after which it splits to form the deep and superficial peroneal nerves. The superficial, fixed location at the fibular neck makes the common peroneal nerve susceptible to compression. The classic cause of traumatic peroneal neuropathy is crush injury from a car bumper striking the lateral aspect of the leg at the knee. Symptoms of common peroneal neuropathy include foot drop (weakness of the tibialis anterior), eversion weakness, and numbness over the anterolateral surface of the lower leg and dorsum of the foot. In contrast, a foot drop due to L5 radiculopathy spares eversion because the S1 fibers are intact. Surgical exploration of a common peroneal crush lesion is typically a low yield endeavor. Rare cases may be due to compressive fibers or adhesions that may be lysed, with the possibility of return of function.

CEREBROVASCULAR DISEASE

Cerebrovascular disease is the most frequent cause of new, rapid-onset, nontraumatic neurologic deficit. It is far more common than seizures or tumors. Vascular structures are subject to a variety of chronic pathologic processes that compromise vessel wall integrity. Diabetes, high cholesterol, high blood pressure, and smoking are risk factors for vascular disease. These conditions can lead to vascular damage by such mechanisms as atheroma deposition causing luminal stenosis, endothelial damage promoting thrombogenesis, and weakening of the vessel wall resulting in aneurysm formation or dissection. These processes may coexist. For instance, a vessel containing an atheromatous plaque will have a decreased luminal diameter. The plaque also may have compromised endothelium, providing the opportunity for thrombus formation, which can lead to acute total occlusion of the remaining lumen. Aneurysms and dissection often occur in atheromatous vessels. Specific patterns of disease relevant to the cerebrovascular system include atheromatous and thrombotic carotid occlusion, brain ischemia from proximal embolic disease, vessel wall rupture leading to hemorrhage, and rupture of abnormal, thin-walled structures, specifically aneurysms and AVMs.

Ischemic Diseases

Ischemic stroke accounts for approximately 85% of acute cerebrovascular events. Symptoms of acute ischemic stroke vary based on the functions of the neural tissues supplied by the occluded vessel, and the presence or absence of collateral circulation. The circle of Willis provides extensive collateral circulation, as it connects the right and left carotid arteries to each other and each to the vertebrobasilar system. Patients with complete occlusion of the carotid artery proximal to the circle of Willis may be asymptomatic if the blood flow patterns can shift and provide sufficient circulation to the ipsilateral cerebral hemisphere from the contralateral carotid and the basilar artery. However, the anatomy of the circle of Willis is highly variable. Patients may have a hypoplastic or missing communicating artery with resultant bilateral ACA supply by one carotid; or the PCA may be supplied by the carotid artery rather than the basilar. Similarly, one vertebral artery is often dominant and the other is hypoplastic. These variations may make disease in a particular vessel more neurologically devastating than in a

patient with full collateral circulation. Occlusion distal to the circle of Willis generally results in a stroke in the territory supplied by that particular artery.

Neurologic deficit from occlusive disease may be temporary or permanent. A patient with sudden-onset focal neurologic deficit that resolves within 24 hours has had a transient ischemic attack. A patient with permanent deficit has had a completed stroke.

Thrombotic Disease

The most common area of neurologically significant vessel thrombosis is the carotid artery in the neck. Disease occurs at the carotid bifurcation. Thrombosis of a carotid artery chronically narrowed by atheroma can lead to acute carotid occlusion. As discussed previously, this can be asymptomatic. The more common concern is thromboembolus. Intracranial arterial occlusion by local thrombus formation may occur, but it is rare compared to embolic occlusion.

Management. Complete occlusion of the carotid artery without referable neurologic deficit requires no treatment. A patient with new neurologic deficit and an angiographically confirmed complete carotid occlusion contralateral to the symptoms should be considered for emergent carotid endarterectomy.²⁴ Surgery should be performed within 2 hours of symptom onset. This time restriction significantly reduces the number of candidates. Surgery should not be performed on obtunded or comatose patients. This time restriction significantly reduces the number of candidates.

Embolic Disease

Emboli causing strokes may originate from a number of sources, including: the left atrium, during atrial fibrillation, a hypokinetic left ventricular wall segment, valvular vegetations, an atheromatous aortic arch, stenotic/atheromatous carotid bifurcations, or from the systemic venous system in the presence of a right-to-left shunt, such as a patent foramen ovale. The majority of emboli enter the anterior (carotid) circulation rather than the posterior (vertebrobasilar) circulation. Characteristic clinical syndromes result from embolic occlusion of the various vessels.

Common Types of Strokes

Anterior Cerebral Artery Stroke The ACA supplies the medial frontal and parietal lobes, including the motor strip, as it courses into the interhemispheric fissure. ACA stroke results in contralateral leg weakness.

Middle Cerebral Artery Stroke The MCA supplies the lateral frontal and parietal lobes and the temporal lobe. MCA stroke results in contralateral face and arm weakness. Dominant-hemisphere MCA stroke causes language deficits. Proximal MCA occlusion with ischemia and swelling in the entire MCA territory can lead to significant intracranial mass effect and midline shift (see Fig. 42-6).

Posterior Cerebral Artery Stroke The PCA supplies the occipital lobe. PCA stroke results in a contralateral homonymous hemianopsia (see Fig. 42-6).

Posterior Inferior Cerebellar Artery Stroke The PICA supplies the lateral medulla and the inferior half of the cerebellar hemispheres. PICA stroke results in nausea, vomiting, nystagmus, dysphagia, ipsilateral Horner's syndrome, and ipsilateral limb ataxia. The constellation of symptoms resulting from PICA occlusion is referred to as the *lateral medullary* or *Wallenberg's syndrome*.

Management. Ischemic stroke management has two goals: reopen the occluded vessel and maintain blood flow to ischemic "penumbra" tissues bordering the vascular territory. Reopening the vessel may be attempted with recombinant tPA.²⁵ tPA administration within 3 hours of the onset of neurologic deficit improves outcome at 3 months. In the setting of suspected ischemic stroke, a head CT must be performed immediately to differentiate ischemic from hemorrhagic stroke. Intracranial hemorrhage, major surgery within the previous 2 weeks, GI or genitourinary hemorrhage in the previous 3 weeks, platelet count less than 100,000/ μ L, and systolic blood pressure >185 mmHg are among the contraindications to tPA therapy.

Patients not eligible for tPA require hemodynamic optimization and neurologic monitoring. Admit such patients to the ICU stroke service for blood pressure management and frequent neurologic checks. Permissive hypertension allows for maximal cerebral perfusion. Systolic blood pressure >180 mmHg may require treatment, but the optimal mean arterial pressure goal is between 100 to 140 mmHg. Give normal saline solution without glucose (which could injure neurons in the penumbra), and aim for normovolemia. A stroke patient who worsens clinically should undergo repeat head CT to evaluate for hemorrhage or increasing mass effect from swelling, which typically peaks 3 to 5 days after the stroke. Significant swelling from an MCA or cerebellar strokes may cause herniation and brain stem injury. A decompressive hemicraniectomy or suboccipital craniectomy can be a life-saving intervention for these select stroke patients.

Hemorrhagic Diseases

Intracranial hemorrhage from abnormal or diseased vascular structures accounts for approximately 15% of acute cerebrovascular events. Hypertension and amyloid angiopathy account for most intraparenchymal hemorrhages, although AVMs, aneurysms, venous thrombosis, tumors, hemorrhagic conversion of ischemic infarct, and fungal infections also may be the cause. The term *intracranial hemorrhage* frequently is used to mean intraparenchymal hemorrhage and will be used here. Intracranial hemorrhage causes local neuronal injury and dysfunction and also may cause global dysfunction due to mass effect if sufficiently large. AVM or aneurysm rupture results in SAH because the major cerebral and cortical blood vessels travel in the subarachnoid space, between the pia and the arachnoid membrane. SAH can cause immediate concussive-like neuronal dysfunction by exposure of the brain to intra-arterial pressure pulsations during the hemorrhage; it can cause delayed ischemia from cerebral arterial vasospasm. Patients presenting with intracranial hemorrhages that do not follow typical patterns should undergo angiography or MRI to evaluate for possible underlying lesions, such as AVM or tumor.

Hemorrhagic stroke typically occurs within the basal ganglia or cerebellum. The patient is usually hypertensive on admission and has a history of poorly controlled hypertension. Such patients are more likely to present with lethargy or obtundation, compared to those who suffer an ischemic stroke. Depressed mental status results from brain shift and herniation secondary to mass effect from the hematoma in deep structures. Ischemic stroke does not cause mass effect acutely; and therefore, patients are more likely to present with normal consciousness and a focal neurologic deficit. Hemorrhagic strokes tend to present with a relatively gradual decline in neurologic function as the hematoma expands, rather than the immediately maximal symptoms caused by ischemic stroke. Table 42-3 provides a

Table 42-3

Anatomic distribution of intracranial hemorrhages and correlated symptoms

% OF INTRACRANIAL HEMORRHAGES	LOCATION	CLASSIC SYMPTOMS
50	Basal ganglia (putamen, globus pallidus), internal capsule	Contralateral hemiparesis
15	Thalamus	Contralateral hemisensory loss
10–20	Cerebral white matter (lobar)	Depends on location (weakness, numbness, partial loss of visual field)
10–15	Pons	Hemiparesis; may be devastating
10	Cerebellum	Lethargy or coma due to brain stem compression and/or hydrocephalus
1–6	Brain stem (excluding pons)	Often devastating

listing of relative incidences of intracranial hemorrhage by anatomic distribution

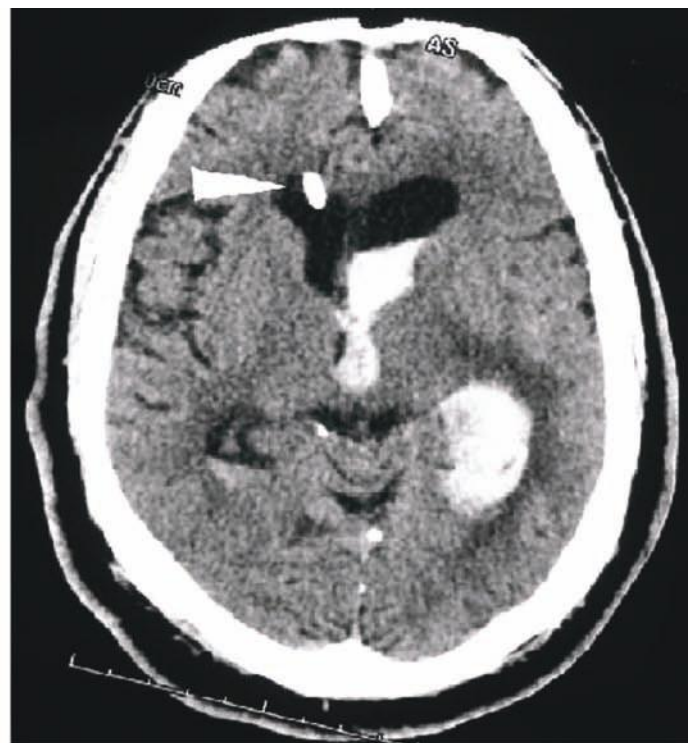
Hypertension. Hypertension increases the relative risk of intracranial hemorrhage by approximately fourfold, likely due to chronic degenerative vasculopathy. Hypertensive hemorrhages often present in the basal ganglia, thalamus, or pons, and result from breakage of small perforating arteries that branch off of much larger parent vessels (Fig. 42-15).

Most hypertensive hemorrhages should be medically managed. The hematoma often contains intact, salvageable axons because the blood dissects through and along neural tracts, and

surgical clot evacuation destroys these axons. Factors potentially favoring surgery include: superficial clot location, young age, nondominant hemisphere, rapid deterioration, and significant mass effect. However, the most comprehensive randomized clinical trials to date did not show an overall improved outcome in surgically evacuated intracranial hemorrhage, except for the subgroup of patients with clot <1 cm from the cortical surface.²⁶ Medical management includes moderate blood pressure control, normalizing platelet and clotting function, phenytoin, and electrolyte management. Intubate patients who cannot clearly follow commands to prevent aspiration and hypercarbia. Follow and



A



B

Figure 42-15. A. Head computed tomography scan of a patient with left-sided weakness and progressive lethargy reveals a right basal ganglia hemorrhage (arrowhead). The blood clot is bright white. Hypodensity around the clot represents cerebral edema. There is blood within the ventricular system. B. Another patient with intraventricular extension of a basal ganglia hemorrhage. The patient developed right-sided weakness and then lethargy. Head computed tomography indicated hydrocephalus. A ventriculostomy was placed for cerebrospinal fluid drainage (arrowhead indicates cross-sectional view of the catheter entering the anterior horn of the right lateral ventricle).

document the neurologic examination and communicate with the family regarding appropriateness for rehabilitation vs withdrawal of care.

Amyloid Angiopathy. The presence of pathologic amyloid deposition in the media of small cortical vessels compromises vessel integrity and tends to cause more superficial (lobar) hemorrhages than hypertensive intracranial hemorrhage. Amyloid laden vessels may hemorrhage multiple times. The superficial location of amyloid hemorrhages may make surgical evacuation less morbid compared to typical deep hypertensive hemorrhages. Nonetheless, medical management and family counseling should be approached similarly to patients with hypertensive hemorrhages.

Cerebral Aneurysm. An aneurysm is a focal dilatation of the vessel wall and is most often a balloon-like outpouching, but may also be fusiform. Aneurysms usually occur at branch points of major vessels (e.g., internal carotid artery bifurcation), or at the origin of smaller vessels (e.g., posterior communicating artery or ophthalmic artery). Approximately 85% of aneurysms arise from the anterior circulation (carotid) and 15% from the posterior circulation (vertebrobasilar). Table 42-4 shows the percentage distribution of cerebral aneurysms by location. Aneurysms are thin walled and at risk for rupture. The major cerebral vessels, and therefore aneurysms, lie in the subarachnoid space. Rupture results in SAH. The aneurysmal tear may be small and seal quickly, or it may not. SAH may consist of a thin layer of blood in the CSF spaces, or thick layers of blood around the brain and extending into brain parenchyma, resulting in a clot with mass effect. Because the meningeal linings of the brain are sensitive, SAH usually results in a sudden, severe “thunderclap” headache. A patient will classically describe “the worst headache of my life.” Presenting neurologic symptoms may range from mild headache to coma to sudden death. The Hunt-Hess grading system categorizes patients clinically (Table 42-5).

Patients with symptoms suspicious for SAH should have a head CT immediately. Acute SAH appears as a bright signal in the fissures and CSF cisterns around the base of the brain, as shown in Fig. 42-16. CT is rapid, noninvasive, and approximately 95% sensitive. In patients with suspicious symptoms but negative head CT, a lumbar puncture (LP) should be

Table 42-4	
Prevalence of cerebral aneurysm by location	
PREVALENCE	ANEURYSM LOCATION (VERNACULAR NAME)
Anterior circulation 85%	30% Anterior communicating artery (A-Comm)
	25% Posterior communicating artery (P-Comm)
	20% Middle cerebral artery bifurcation
	10% Other
Posterior circulation 15%	10% Basilar artery, most frequently at the basilar tip
	5% Vertebral artery, usually at the posterior inferior cerebellar artery

Table 42-5
The Hunt-Hess clinical grading system for subarachnoid hemorrhage

HUNT-HESS GRADE	CLINICAL PRESENTATION
0	Asymptomatic; unruptured aneurysm
1	Awake; asymptomatic or mild headache; mild nuchal rigidity
2	Awake; moderate to severe headache, cranial nerve palsy (e.g., cranial nerve III or IV), nuchal rigidity
3	Lethargic; mild focal neurologic deficit (e.g., pronator drift)
4	Stuporous; significant neurologic deficit (e.g., hemiplegia)
5	Comatose; posturing

performed. An LP with xanthochromia and high red blood cell counts (usually 100,000/mL), which do not decrease between tubes 1 and 4, is consistent with SAH. Negative CT and LP essentially rules out SAH. Patients diagnosed with SAH



Figure 42-16. Head computed tomography scan of a patient who experienced a sudden, severe headache. Subarachnoid hemorrhage is visible as hyperdense signal in the interhemispheric fissure (1), bilateral sylvian fissures (2 shows the left fissure), and in the ambient cisterns around the midbrain (3). This gives the classic five-pointed-star appearance of a subarachnoid hemorrhage. Visible temporal tips of the lateral ventricles indicate hydrocephalus.

require four-vessel cerebral angiography within 24 hours to assess for aneurysm or other vascular malformation. Catheter angiography remains the gold standard for assessing the patient's cerebral vasculature, relevant anomalies, and presence, location, and morphology of the cerebral aneurysms. Figure 42-17A demonstrates the typical anteroposterior digital subtraction angiographic view of a cerebral aneurysm. Figure 42-17B shows the anatomy of the circle of Willis in a simplified graphic representation to assist in visualizing the locations of various cerebral aneurysms.

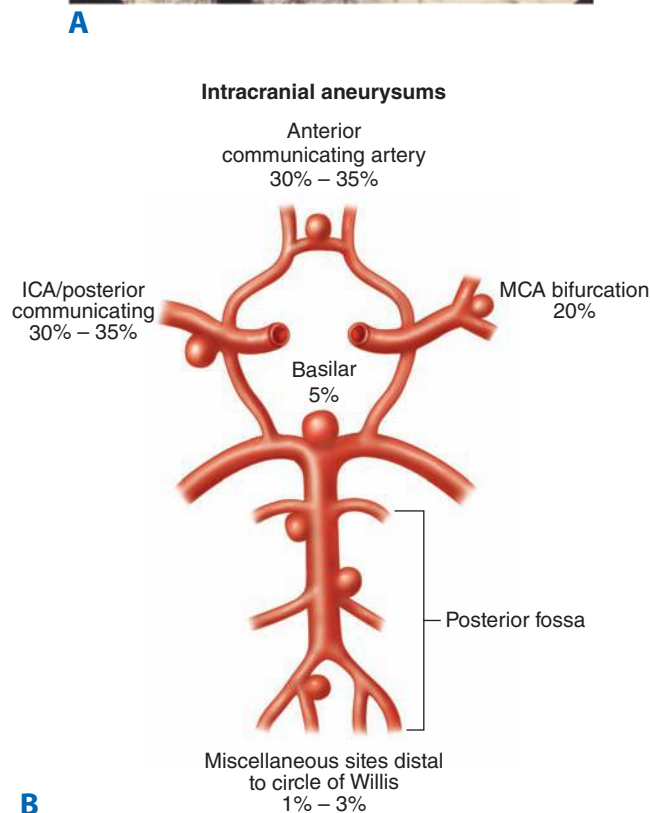
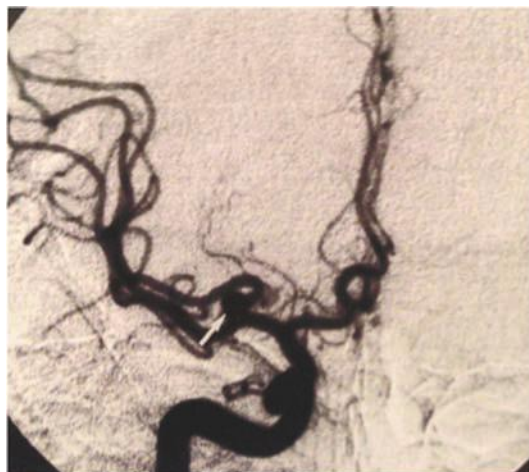


Figure 42-17. A. Anteroposterior view after injection of contrast dye in the right internal carotid artery demonstrates an aneurysm of the middle cerebral artery bifurcation. B. Figure depicting the anatomy of the circle of Willis and the common sites for aneurysms. ICA = internal cerebral artery; MCA = middle cerebral artery. (Reproduced with permission from Osborn AG: *Handbook of Neuroradiology: Brain and Skull, 1st ed.* St. Louis: Mosby-Year Book, Inc., 1991, p 81. Copyright Elsevier.)

SAH patients should be admitted to the neurologic ICU. Hunt-Hess grade 4 and 5 patients require intubation and hemodynamic monitoring and stabilization. The current standard of care for ruptured aneurysms requires early aneurysmal occlusion. There are two options for occlusion. The patient may undergo craniotomy with microsurgical dissection and placement of a titanium clip across the aneurysm neck to exclude the aneurysm from the circulation and reconstitute the lumen of the parent vessel. The second option is to “coil” the aneurysm via an endovascular approach. The patient is taken to the interventional neuroradiology suite for placement of looped titanium coils inside the aneurysm dome. The coils support thrombosis and prevent blood flow into the aneurysm. Factors favoring craniotomy and clipping include young age, good medical condition, and broad aneurysm necks. Factors favoring coiling include age, medical comorbidities, and narrow aneurysm necks. Due to coil migration or compaction over time, surgical clipping is believed to result in a more definitive cure. The decision to clip or coil is complex and should be fully explored. The International Subarachnoid Aneurysm Trial researchers suggested that endovascular occlusion resulted in better outcomes for certain types of cerebral aneurysms, although this trial was marred by poor selection and randomization techniques, and the validity of its conclusions have been questioned.²⁷ Long-term outcomes may be better in younger patients with clipped aneurysms.²⁸ Debate also continues regarding optimal care for unruptured intracranial aneurysms.²⁹

SAH patients often require 1 to 3 weeks of ICU care after aneurysm occlusion for medical complications that accompany neurologic injury. In addition to routine ICU concerns, SAH patients are also at risk for cerebral vasospasm. In vasospasm, cerebral arteries constrict pathologically and can cause ischemia or stroke from 4 to 21 days after SAH. Current vasospasm prophylaxis includes maintenance of optimal perfusion with hypertension and mild hypervolemia, as well as administration of nimodipine, a calcium channel blocker that may decrease the incidence and degree of spasm. Neurointerventional options for treating symptomatic vasospasm include intra-arterial papaverine or nicardipine, and balloon angioplasty for larger caliber vessels.

Aneurysmal SAH has an approximate mortality rate of 50% in the first month. Approximately one-third of survivors return to pre-SAH function, and the remaining two thirds have mild to severe disability. Most require rehabilitation after hospitalization.

Arteriovenous Malformations. AVMs are abnormal, dilated arteries and veins without an intervening capillary bed. The nidus of the AVM contains a tangled mass of vessels but no neural tissue. AVMs may be asymptomatic or present with SAH, intraparenchymal hemorrhage, or seizures. Small AVMs present with hemorrhage more often than large AVMs, which tend to present with seizures. Headache, bruit, or focal neurologic deficits are less common symptoms. AVMs hemorrhage at an average rate of 2% to 4% a year. Figure 42-18 demonstrates the angiographic appearance of an AVM in arterial and venous phases.

There are several management differences for intracranial hemorrhage due to AVM vs. aneurysm. Definitive therapy for the AVM usually is delayed 3 to 4 weeks to allow the brain to recover from acute injury. There is less risk of devastating early rebleeding from AVMs, and vasospasm is much less common. Three therapeutic modalities for AVMs are currently in common use: microsurgical excision, interventional radiology or endovascular embolization, and stereotactic radiosurgery

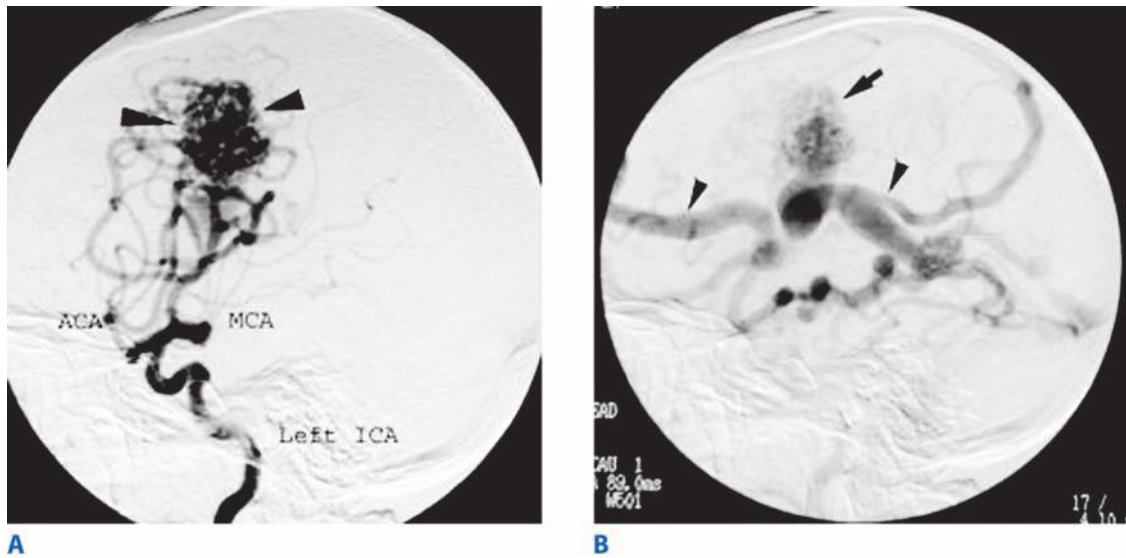


Figure 42-18. **A.** Lateral view after injection of contrast dye in the left internal carotid artery demonstrates a 3×4 cm left frontal arteriovenous malformation indicated by *arrowheads*. This image was taken 1.06 seconds after dye injection, and is referred to as an *arterial phase image*. **B.** Same view taken 4.10 seconds after dye injection, providing a *venous phase image*. The *arrow* points to the arteriovenous malformation nidus. The *arrowheads* indicate two pathologically enlarged draining veins. ACA = anterior cerebral artery; ICA = internal carotid artery; MCA = middle cerebral artery.

(SRS). AVMs that are large, near eloquent cortex, or that drain to deep venous structures are considered high grade and more difficult to surgically resect without causing a significant neurologic deficit. Radiosurgery can treat these lesions, although it is limited to lesions <3 cm in diameter and has a 2-year lag time (i.e., the AVM may bleed in the interval). Embolization reduces flow through the AVM. It is usually considered adjunctive therapy, but it may serve as the sole treatment for deep, inaccessible lesions.

TUMORS OF THE CENTRAL NERVOUS SYSTEM

A wide variety of tumors affect the brain and spine. Primary benign and malignant tumors arise from the various elements of the CNS, including neurons, glia, and meninges. Tumors metastasize to the CNS from many primary sources. Presentation varies widely depending on relevant neuroanatomy. **5►** Prognosis depends on histology and anatomy. Modern brain tumor centers use team approaches to CNS tumors, as patients may require a combination of surgery, radiation therapy, chemotherapy, SRS, and research protocol enrollment. Tumors affecting the peripheral nervous system are discussed in the Peripheral Nerve section.

Intracranial Tumors

Intracranial tumors can cause brain injury from mass effect, dysfunction or destruction of adjacent neural structures, swelling, or abnormal electrical activity (seizures). Supratentorial tumors commonly present with focal neurologic deficit, such as contralateral limb weakness, visual field deficit, headache, or seizure. Infratentorial tumors often cause increased ICP due to hydrocephalus from compression of the fourth ventricle, leading to headache, nausea, vomiting, or diplopia. Cerebellar hemisphere or brain stem dysfunction can result in ataxia, nystagmus, or cranial nerve palsies. Infratentorial tumors rarely cause seizures.

All patients with symptoms concerning for brain tumor should undergo MRI with and without gadolinium. Initial man-

agement of a patient with a symptomatic brain tumor generally includes dexamethasone for reduction of vasogenic edema and phenytoin if the patient has seized. Patients with significant weakness, lethargy, or hydrocephalus should be admitted for observation until definitive care is administered.

Metastatic Tumors

Prolonged cancer patient survival and improved CNS imaging have increased the likelihood of diagnosing cerebral metastases. The sources of most cerebral metastases are (in decreasing frequency): lung, breast, kidney, GI tract, and melanoma. Lung and breast cancers account for more than half of cerebral metastases. Metastatic cells usually travel to the brain hematogenously and frequently seed the gray-white junction. Other common locations are the cerebellum and the meninges. Meningeal involvement may result in carcinomatous meningitis, also known as *leptomeningeal carcinomatosis*. MRI pre- and postcontrast administration is the study of choice for evaluation. Figure 42-19 demonstrates bilateral cerebellar metastases. These lesions are typically well circumscribed, round, and multiple. Such findings should prompt a metastatic work-up, including CT scan of the chest, abdomen, and pelvis, and a bone scan.

Management largely depends upon the primary tumor, overall tumor burden, patient's medical condition, and location and number of metastases. The beliefs of the patient and family regarding aggressive care must be considered. Craniotomy plus whole-brain radiation therapy (WBRT) or stereotactic radiosurgery (SRS) to the tumor bed has been shown to benefit patients with a single surgically accessible metastatic lesion, compared to radiation therapy alone. Median survival increased from 15 to 40 weeks in one randomized trial.³⁰ Postoperative radiotherapy may not increase overall survival but it does significantly reduce original lesion recurrence.³¹ Studies do not support craniotomy unless all detectable metastases can be resected. Recent data suggest that SRS (e.g., gamma knife) may be applied to multiple metastases in one session with improved outcome.³²

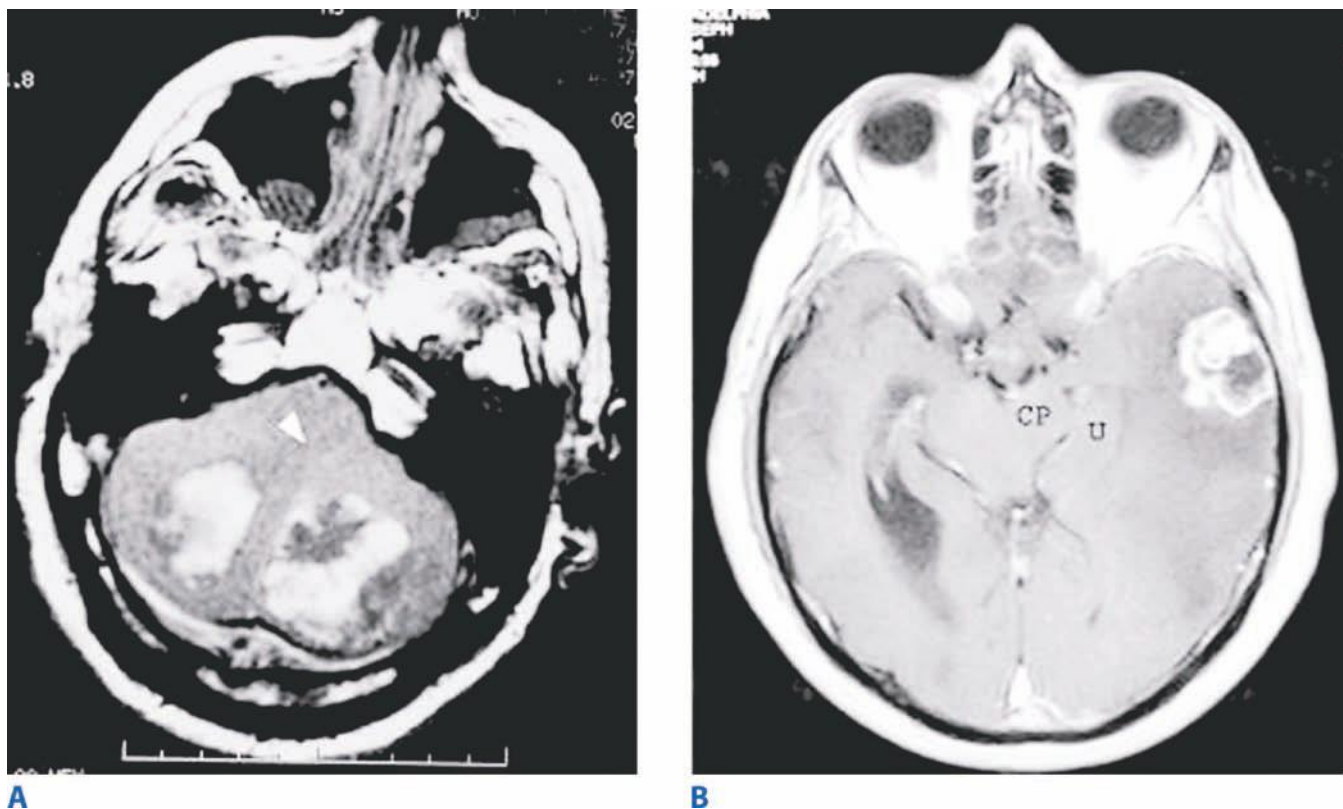


Figure 42-19. **A.** Precontrast T1-weighted axial magnetic resonance imaging demonstrating bilateral hemorrhagic cerebellar metastases. Patient presented with ataxia and then lethargy progressing to deep coma. This patient has total effacement of the fourth ventricle and severe brain stem compression. The fourth ventricle cerebrospinal fluid space should be at the tip of the *arrowhead*. Patient recovered to normal mental status after emergent posterior fossa craniotomy. **B.** Postcontrast T1-weighted axial magnetic resonance imaging demonstrating a ring-enhancing lesion in the lateral left temporal lobe with moderate edema. The uncus (*U*) is compressing the left cerebral peduncle (*CP*) and displacing the brain stem to the right.

Glial Tumors

Glial cells provide the anatomic and physiologic support for neurons and their processes in the brain. The several types of glial cells give rise to distinct primary CNS neoplasms.

Astrocytoma. Astrocytoma is the most common primary CNS neoplasm. The term *glioma* often is used to refer to astrocytomas specifically, excluding other glial tumors. Astrocytomas are graded from I to IV. Grades I and II are referred to as low-grade astrocytoma, grade III as anaplastic astrocytoma, and grade IV as glioblastoma multiforme (GBM). Prognosis varies significantly between grades I/II, III, and IV, but not between I and II. Median survival is 8 years after diagnosis with a low-grade tumor, 2 to 3 years with an anaplastic astrocytoma, and roughly 1 year with a GBM. GBMs account for almost two-thirds of all astrocytomas, anaplastic astrocytomas account for two-thirds of the rest, and low-grade astrocytomas the remainder. Figure 42-20 demonstrates the typical appearance of a GBM.

The great majority of astrocytomas infiltrate adjacent brain. Juvenile pilocytic astrocytomas and pleomorphic xanthoastrocytomas are exceptions. These tumors are circumscribed, low grade, and associated with a good prognosis. Histologic features associated with higher grade include hypercellularity, nuclear atypia, and endovascular hyperplasia. Necrosis is present only with GBMs; it is required for the diagnosis.

Gross total resection should be attempted for suspected astrocytomas. Motor cortex, language centers, deep or midline

structures, or brain stem location may make this impossible without unacceptable, devastating neurologic deficit. Such lesions may be limited to stereotactic needle biopsy specimen. Gross total resection followed by radiation therapy improves survival for all grades, although radiation therapy may be delayed until recurrence in low-grade tumors. Chemotherapy such as temozolomide is of limited efficacy and typically is reserved for GBM. There are various ongoing research studies for GBM adjuvant therapy; these should be discussed with the patient and family. Other options include Iotrex-containing balloons for conformal radiation brachytherapy (Glia-Site), placed in the resection cavity at the time of surgery for recurrence. Adjuvant therapy remains marginally effective; survival has changed little over the last several decades.

Oligodendroglioma. Oligodendroglioma accounts for approximately 10% of gliomas. They often present with seizures. Calcifications and hemorrhage on CT or MRI suggest the diagnosis. Oligodendrogliomas are also graded from I to IV; grade portends prognosis. Prognosis is better overall than for astrocytomas. Median survival ranges from 2 to 7 years for highest and lowest grade tumors, respectively. Aggressive resection improves survival. Many oligodendrogliomas will respond to procarbazine, lomustine (CCNU), vincristine (PCV) chemotherapy. A particular chromosomal deletion, 1p19q, has been associated with robust response to the chemotherapeutic agent temozolomide. Radiation has not been clearly shown to prolong survival.

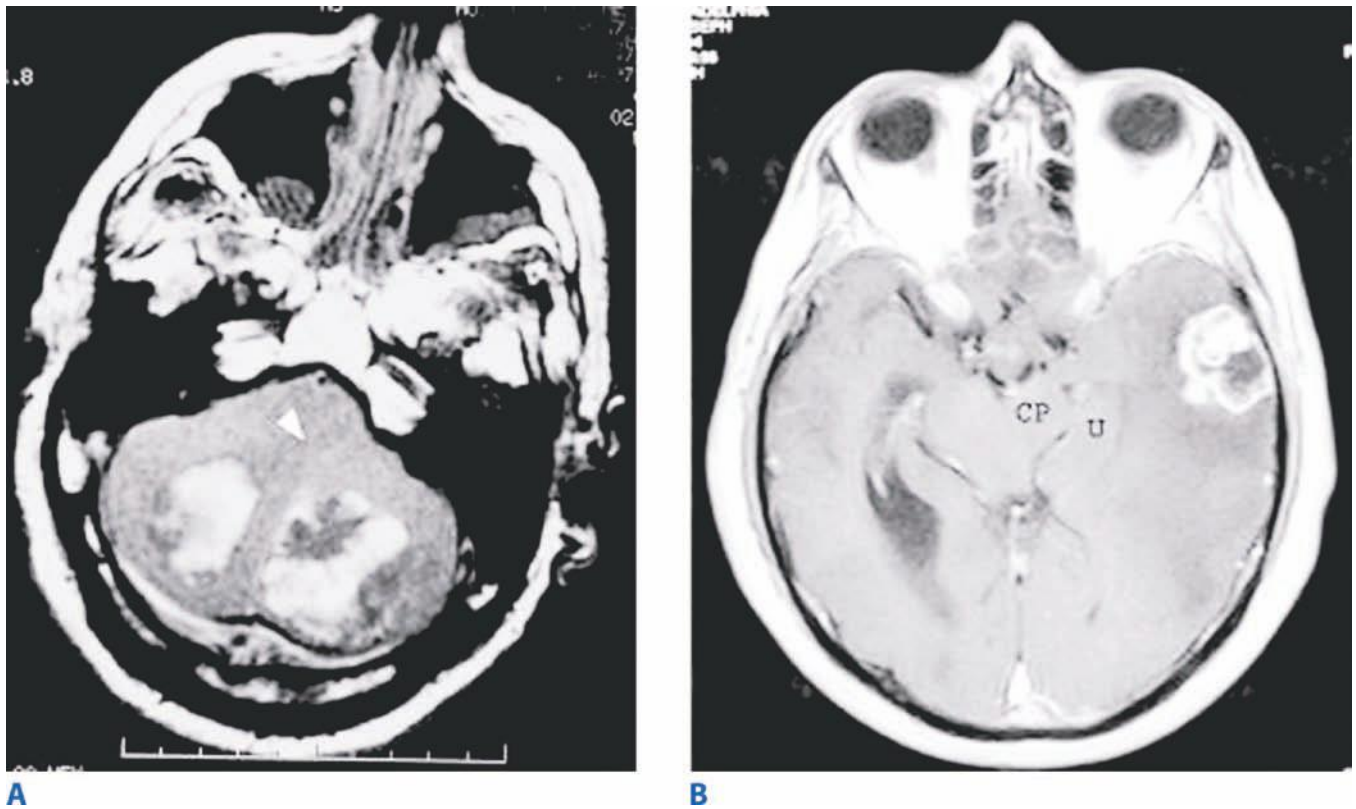


Figure 42-20. A. Postcontrast T1-weighted axial magnetic resonance imaging demonstrating a ring-enhancing lesion in the anteromedial right temporal lobe with central necrosis (dark area) consistent with glioblastoma multiforme. B. T2-weighted axial magnetic resonance imaging with extensive bright signal signifying peritumoral edema seen with glioblastoma multiformes.

Ependymoma. The lining of the ventricular system consists of cuboidal/columnar ependymal cells from which ependymomas may arise. Although most pediatric ependymomas are supratentorial, two-thirds of adult ependymomas are infratentorial. Supratentorial ependymomas arise from the lateral or third ventricles. The infratentorial tumors arise from the floor of the fourth ventricle (i.e., off the posterior brain stem). The most common symptoms are headache, nausea, vomiting, or vertigo, secondary to increased ICP from obstruction of CSF flow through the fourth ventricle. The tumors may grow out the foramina of Luschka to form a cerebellopontine angle mass. They may also spread through the CSF to form “drop mets” in the spinal canal. The two main histologic subtypes are papillary and anaplastic, the latter characterized by increased mitotic activity and areas of necrosis. Gross total resection often is impossible because the tumor arises from the brain stem. The goal of surgery is to achieve maximal resection without injuring the very delicate brain stem. Suboccipital craniotomy and midline separation of the cerebellar hemispheres allows access to tumors in the fourth ventricle. Postoperative radiation therapy significantly improves survival. Patients with CSF spread documented by LP or contrast MRI should also have whole-spine radiation plus focused doses to visualized metastases.

Choroid Plexus Papilloma. The choroid plexus is composed of many small vascular tufts covered with cuboidal epithelium. It represents part of the interface between blood and brain. The choroid cells create CSF from blood and release it into the ventricular system. Choroid plexus papillomas and

choroid plexus carcinomas (rare, mostly pediatric) may arise from these cells. Papillomas usually occur in infants (typically supratentorial in the lateral ventricle) but also occur in adults (usually infratentorial in the fourth ventricle). Papillomas are well circumscribed and vividly enhance due to extensive vasculature. Like ependymomas, adult choroid plexus papillomas usually present with symptoms of increased ICP. Treatment is surgical excision. Total surgical excision is curative; recurrent papillomas should be re-resected. Radiation or chemotherapy are not indicated for papillomas. Radiation is adjunctive to aggressive surgery for carcinomas, but the results are generally poor.

Neural Tumors and Mixed Tumors

Neural and mixed tumors are a diverse group that includes tumors variously containing normal or abnormal neurons and/or normal or abnormal glial cells. Primitive neuroectodermal tumors arise from bipotential cells, capable of differentiating into neurons or glial cells.

Medulloblastoma. Primitive neuroectodermal tumor is the most common type of medulloblastoma. Most occur in the first decade of life, but there is a second peak around age 30. Medulloblastoma is the most common malignant pediatric brain tumor. They are usually midline. Most occur in the cerebellum and present with symptoms of increased ICP. Histologic characteristics include densely packed small round cells with large nuclei and scant cytoplasm. They are generally not encapsulated, frequently disseminate within the CNS, and should undergo surgical resection followed by radiation therapy and chemotherapy.

Ganglioglioma. Ganglioglioma is a mixed tumor in which both neurons and glial cells are neoplastic. They occur in the first three decades of life, often in the medial temporal lobe, as circumscribed masses that may contain cysts or calcium and may enhance. The presenting symptom is usually a seizure, due to the medial temporal location. Patients have a good prognosis after complete surgical resection.

Neural Crest Tumors

Multipotent neural crest cells develop into a variety of disparate cell types, including smooth muscle cells, sympathetic and parasympathetic neurons, melanocytes, Schwann cells, and arachnoid cap cells. They migrate in early development from the primitive neural tube throughout the body.

Miscellaneous Tumors

Meningioma. Meningiomas are derived from arachnoid cap cells of the arachnoidea mater. They appear to arise from the dura mater grossly and on MRI and are commonly referred to as *dural-based tumors*. The most common intracranial locations are along the falx (Fig. 42-21), the convexities (i.e., over the cerebral hemispheres), and the sphenoid wing. Less common locations include the foramen magnum, olfactory groove, and inside the lateral ventricle. Most are slow growing, encapsulated, benign tumors. Aggressive atypical or malignant meningiomas may invade adjacent bone or cerebral cortex. Previous

cranial irradiation increases the incidence of meningiomas. Approximately 10% of patients with a meningioma have multiple meningiomas. Total resection is curative, although involvement with small perforating arteries or cranial nerves may make total resection of skull base tumors impossible without significant neurologic deficit. Small, asymptomatic meningiomas can be followed until symptomatic or until significant growth is documented on serial imaging studies. Atypical and malignant meningiomas may require postoperative radiation. Patients may develop recurrences from the surgical bed or distant *de novo* tumors.

Vestibular Schwannoma (Acoustic Neuroma). Vestibular schwannomas predominantly arise from the superior half of the vestibular portion of the vestibulocochlear nerve (cranial nerve VIII) (Fig. 42-22). Commonly, patients present with progressive hearing loss, tinnitus, or balance difficulty. Large tumors may cause brain stem compression and obstructive hydrocephalus. Bilateral acoustic neuromas are pathognomonic for neurofibromatosis type 2 (NF2), a syndrome resulting from mutation of chromosome 22. NF2 patients have an increased incidence of spinal and cranial meningiomas and gliomas.

Vestibular schwannomas may be treated with microsurgical resection or SRS (gamma knife or linear accelerator technology). The main complication with treatment is damage to the facial nerve (cranial nerve VII), which runs through the internal auditory canal with the vestibulocochlear nerve. Risk of facial nerve dysfunction increases with increasing tumor diameter.

Pituitary Adenoma. Pituitary adenomas arise from the anterior pituitary gland (adenohypophysis). Tumors <1 cm diameter are considered microadenomas; larger tumors are macroadenomas. Pituitary tumors may be functional (i.e., secrete endocrinologically active compounds at pathologic levels) or nonfunctional (i.e., secrete nothing or inactive compounds). Functional tumors are often diagnosed when quite small, due to endocrine dysfunction. The most common endocrine syndromes are Cushing's disease, due to adrenocorticotrophic hormone secretion, Forbes-Albright syndrome, due to prolactin secretion, and acromegaly, due to growth hormone secretion. Nonfunctional tumors are typically diagnosed as larger lesions causing mass effects such as visual field deficits due to compression of the optic chiasm or panhypopituitarism due to compression of the gland. Figure 42-23 demonstrates a large pituitary adenoma. Hemorrhage into a pituitary tumor causes abrupt symptoms of headache, visual disturbance, decreased mental status, and endocrine dysfunction. This is known as *pituitary apoplexy*.

Symptomatic pituitary tumors should be decompressed surgically to eliminate mass effect and/or to attempt an endocrine cure. However, prolactin-secreting tumors (prolactinomas) usually shrink with dopaminergic therapy alone, namely bromocriptine, which inhibits production and secretion of prolactin. Consider surgery for prolactinomas with persistent mass effect or endocrinologic dysfunction in spite of adequate dopamine agonist therapy. Most pituitary tumors are approached through the nose via the transsphenoidal approach, and minimally invasive, endoscopic surgical techniques are being used increasingly.

Hemangioblastoma. Hemangioblastomas occur almost exclusively in the posterior fossa, with about 20% occurring in patients with von Hippel-Lindau (VHL) disease, a multisystem neoplastic disorder. Other tumors associated with VHL are renal cell

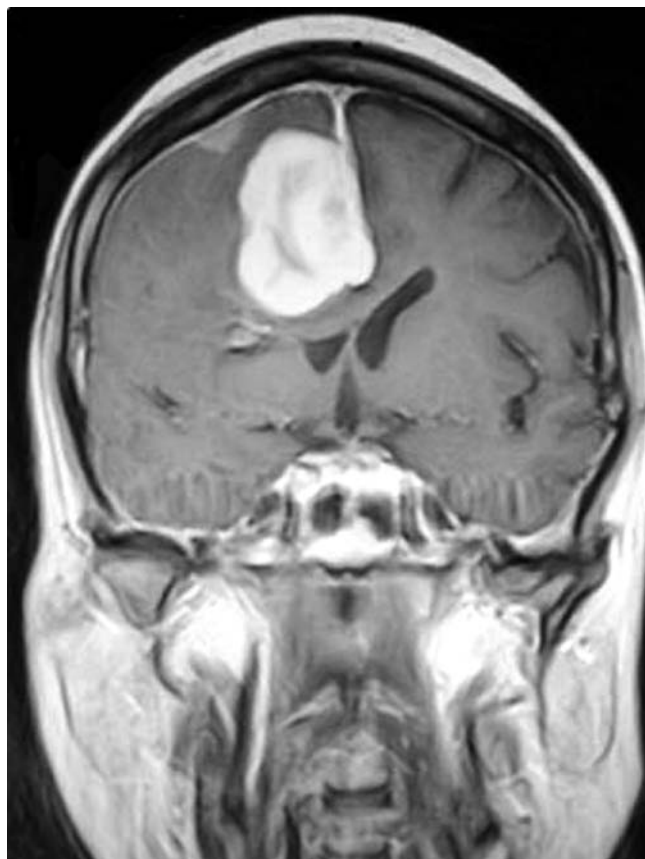
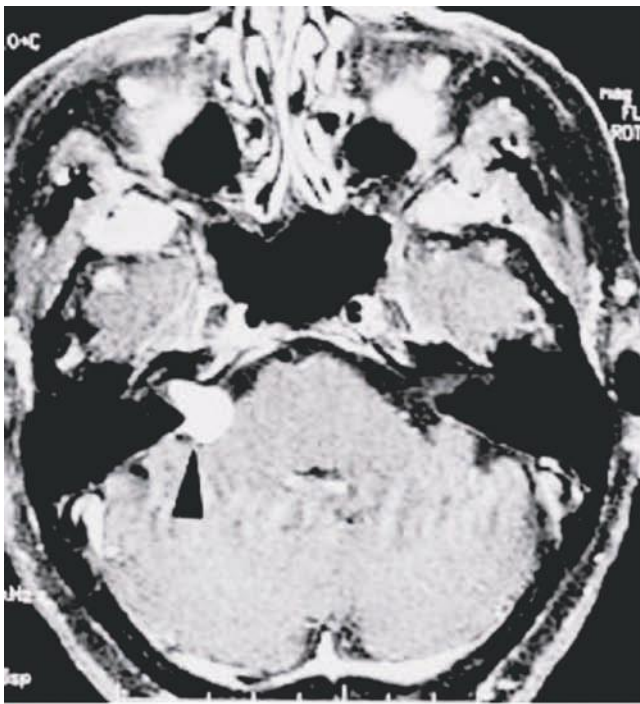


Figure 42-21. Postcontrast T1-weighted coronal magnetic resonance imaging demonstrating a brightly enhancing lesion arising from the falx cerebri with moderate edema and mass effect on the right lateral ventricle. This is a falcine meningioma. Note also the small separate meningioma arising from the dura over the cerebral convexity.



A



B

Figure 42-22. A. Postcontrast T1-weighted axial magnetic resonance imaging demonstrating a brightly enhancing mass on the right vestibular nerve with an enhancing tail going into the internal auditory canal (*arrowhead*). Pathology demonstrated vestibular schwannoma. B. Postcontrast T1-weighted sagittal magnetic resonance imaging of the same lesion, indicated by the *arrowhead*. Note small incidental meningioma at the top of the scan.



Figure 42-23. Postcontrast T1-weighted sagittal magnetic resonance imaging demonstrating a large sellar/suprasellar lesion (*arrowheads*) involving the third ventricle superiorly and abutting the midbrain and pons posteriorly. The patient presented with progressive visual field and acuity loss. Pathology and lab work revealed a nonfunctioning pituitary adenoma.

carcinoma, pheochromocytoma, and retinal angiomas. Many appear as cystic tumors with an enhancing tumor on the cyst wall known as the *mural nodule*. Surgical resection is curative for sporadic (non-VHL associated) tumors. Pathology reveals abundant thin-walled vascular channels; internal debulking may be bloody. En bloc resection of the mural nodule alone, leaving the cyst wall, is sufficient.

Lymphoma. CNS lymphoma may arise either primarily in the CNS or secondarily from systemic disease. Recent rising incidence may be due to growing transplant and AIDS populations. Presenting symptoms include mental status changes, headache due to increased ICP, and cranial nerve palsy due to lymphomatous meningitis (analogous to carcinomatous meningitis). Often, lymphoma appears hyperdense on CT due to dense cellularity, and most lesions typically enhance with contrast. Surgical excision is not indicated. A stereotactic needle biopsy specimen usually confirms the diagnosis. Subsequent treatment includes steroids, whole-brain radiation, and chemotherapy. Intrathecal methotrexate is an option.

Embryologic Tumors

Embryologic tumors result from embryonal remnants that fail to involute completely or differentiate properly during development.

Craniopharyngioma. Craniopharyngiomas are benign cystic lesions that occur most frequently in children. There is a second peak of incidence around 50 years of age. Calcification occurs in all pediatric and roughly half of adult craniopharyngiomas. Symptoms result from compression of adjacent structures, especially the optic chiasm. Pituitary or hypothalamic dysfunction or hydrocephalus may develop. Treatment is primarily surgical. Excision is somewhat easier in children, as the tumor is often soft and easily suctioned. Adult tumors are often firm and adherent to adjacent vital structures. Visual loss, pituitary endocrine

hypofunction, diabetes insipidus, and cognitive impairment from basal frontal injury are common complications.

Epidermoid. Epidermoid tumors are cystic lesions with stratified squamous epithelial walls from trapped ectodermal cell rests that grow slowly and linearly by desquamation into the cyst cavity. The cysts contain keratin, cholesterol, and cellular debris (Fig. 42-24). They occur most frequently in the cerebellopontine angle and may cause symptoms due to brain stem compression. Recurrent bouts of aseptic meningitis may occur due to release of irritative cyst contents into the subarachnoid space (Mollaret's meningitis). Treatment is surgical drainage and removal of the cyst wall. Intraoperative spillage of cyst contents may lead to severe chemical meningitis and must be avoided by containment and aspiration.

Dermoid. Dermoids are less common than epidermoid tumors. They contain hair follicles and sebaceous glands in addition to a squamous epithelium. Dermoids may be found anywhere along the craniospinal axis. They are more commonly midline structures and are associated with more anomalies than epidermoids. They may be associated with trauma, as from a lumbar puncture that drags skin structures into the spine. Bacterial meningitis may occur when dermoids are associated with a dermal sinus tract. Treatment of symptomatic lesions is surgical resection, again with care to control cyst contents.

Teratoma. Teratomas are germ cell tumors that arise in the midline, often in the pineal region (the area behind the third ventricle, above the midbrain and cerebellum). They contain elements from all three embryonal layers: ectoderm, meso-

derm, and endoderm. Teratomas may contain skin, cartilage, GI glands, and teeth. Teratomas with more primitive features are more malignant, while those with more differentiated tissues are more benign. Surgical excision may be attempted. However, the prognosis for malignant teratomas is very poor.

Spinal Tumors

A wide variety of tumors affect the spine. Approximately 20% of CNS tumors occur in the spine. Unlike cranial tumors, the majority of spinal tumors are histologically benign. Understanding two major spinal concepts—stability and neural compression—facilitates an understanding of the effects of spinal tumors. Destruction of bones or ligaments can cause spinal instability, leading to deformities such as kyphosis, subluxation, or possible subsequent neural compression. Tumor growth in the spinal canal or neural foramina can cause direct compression of the spinal cord or nerve roots and cause pain and loss of function. Classically, the pain is worse at night. Anatomic categorization provides the most logical approach to these tumors. Certain tumors present in characteristic locations. An understanding of the anatomy leads to an understanding of the clinical presentation and possible therapeutic options.

Extradural Tumors. Extradural tumors account for approximately 55% of spinal tumors. This category includes tumors arising within the bony vertebral structures and from within the epidural space. Destruction of the bone can lead to instability and fractures, causing pain and/or deformity. Epidural expansion can lead to spinal cord or nerve root compression with myelopathy, radiculopathy, or a combination thereof.

Metastatic Tumors Metastatic tumors are the most common extradural tumors. Spinal metastases most commonly occur in the thoracic and lumbar vertebral bodies because the greatest volume of red bone marrow is found in these regions. The most common primary sources of spine metastasis are lymphoma, lung, breast, and prostate. Other sources include renal, colon, thyroid, sarcoma, and melanoma. Most spinal metastases create osteolytic lesions. Osteoblastic, sclerotic lesions suggest prostate cancer in men and breast cancer in women.

Patients with progressive neurologic dysfunction due to a metastatic lesion should undergo urgent surgery followed by radiation therapy.³³ Patients with debilitating pain may undergo radiation therapy with close observation for neurologic deterioration. Preoperative neurologic function correlates with postoperative function. Patients may lose function over hours. These patients should be given high-dose IV dexamethasone, taken immediately to MRI, and then to the OR or radiation therapy suite. Indications for surgery include failure of radiation therapy, spinal instability, recurrence after radiation therapy, and the need for diagnosis in cases of unknown primary tumors. Most cases with significant bone involvement require both decompression and fusion. Bony fusion usually takes 2 to 3 months. Prognosis governs operative decisions. Surgery is unlikely to improve quality of life for patients with a life expectancy of 3 months or less, but it is likely to improve quality of life for patients with life expectancy of 6 months or more. Benefit for patients with 3- to 6-months life expectancy is unclear and requires frank discussion with the patient and family. Patients who are unlikely to tolerate general anesthesia, are already completely paralyzed, or who have very radiosensitive tumors such as multiple myeloma and lymphoma, should not generally undergo surgery.



Figure 42-24. Postcontrast T1-weighted axial magnetic resonance imaging demonstrating a nonenhancing mass in the left cerebellopontine angle with brain stem compression. White arrowhead indicates interface of tumor and brain stem. Black arrowhead indicates deformed fourth ventricle. Pathology revealed epidermoid tumor.

Primary Tumors Hemangiomas are benign tumors found in 10% of people at autopsy. They occur in the vertebral bodies of the thoracolumbar spine and are frequently asymptomatic. They are often vascular and may hemorrhage, causing pain or neurologic deficit. Large hemangiomas can destabilize the spine and predispose to fracture. Osteoblastic lesions include osteoid osteoma and osteoblastoma. The latter tends to be larger and more destructive. Aneurysmal bone cysts are nonneoplastic, expansile, lytic lesions containing thin-walled blood cavities that usually occur in the lamina or spinous processes of the cervicothoracic spine. They may cause pain or sufficiently weaken the bone to cause a fracture. Cancers arising primarily in the bony spine include Ewing's sarcoma, osteosarcoma, chondrosarcoma, and plasmacytoma.

Intradural Extramedullary Tumors

Intradural extramedullary tumors constitute approximately 40% of spinal tumors and arise from the meninges or nerve root elements. They may compress the spinal cord, causing myelopathy, or the nerve roots, causing radiculopathy. The most common intradural extramedullary tumors are typically benign, slow growing, and well circumscribed. Rare benign epidural masses include arachnoid cysts, dermoids, and epidermoids. Rare malignant epidural tumors include metastases and high-grade gliomas, or "drop" metastases from posterior fossa gliomas.

Meningioma Meningiomas arise from the arachnoidea mater. They appear to be dural based and enhance on MRI. An enhancing "dural tail" may be seen. They occur most commonly in the thoracic spine (Fig. 42-25) but also arise in the cervical and lumbar regions. Some spinal meningiomas grow into the epidural space. Growth causes cord compression and progressive myelopathy with hyperreflexia, spasticity, and gait difficulties. Surgical excision is the treatment of choice. The surgeon often finds a clean margin between the tumor, dura, and spinal cord, allowing en bloc resection without damage to the cord.

Schwannoma Schwannomas are derived from peripheral nerve sheath Schwann cells. They are benign, encapsulated tumors that rarely undergo malignant degeneration. While two-thirds are entirely intradural, one-sixth are entirely extradural, and one-sixth have a classic "dumbbell" shape from intradural and extradural components. Symptoms result from radiculopathy, often presenting as pain or myelopathy. Symptomatic lesions should be surgically resected. The parent nerve root usually can be preserved. Patients with multiple schwannomas likely have NF2. In these patients, a careful neurologic examination is needed to determine which lesions are symptomatic and require resection.

Neurofibroma In contrast to schwannomas, neurofibromas tend to appear more fusiform and to grow within the parent nerve, rather than forming an encapsulated mass branching off the nerve. Neurofibromas are benign but not encapsulated. They present similarly to schwannomas, and the two may be difficult to differentiate on imaging. Salvage of the parent nerve is more challenging with neurofibromas. To improve the likelihood of total resection, thoracic and high cervical nerve roots may be sacrificed with minimal deficit. Patients with multiple neurofibromas likely have NF1, also known as *von Recklinghausen's neurofibromatosis*. Resection for symptomatic lesions should be offered.

Intramedullary Tumors. Intramedullary tumors constitute approximately 5% of spinal tumors. They arise from within the parenchyma of the spinal cord. Common presenting symptoms



Figure 42-25. T2-weighted sagittal magnetic resonance imaging of the midthoracic spine demonstrating a well-encapsulated tumor arising from the dura posteriorly and compressing the spinal cord. Arrowhead points to dorsal location of the mass. The patient presented with worsening gait and lower extremity spasticity. Pathology demonstrated meningioma.

are local dysesthesia, burning pain, radicular pain, sensory loss, weakness, or sphincter dysfunction. Patients with such symptoms should undergo MRI of the entire spine with and without enhancement.

Ependymoma Ependymomas are the most common intramedullary tumors in adults. There are several histologic variants. The myxopapillary type occurs in the conus medullaris or the filum terminale in the lumbar region and has the best prognosis after resection. The cellular type occurs more frequently in the cervical cord. Many spinal ependymomas have cystic areas and may contain hemorrhage. Surgical removal can improve function. A distinct tumor margin often exists, allowing safer excision. Postoperative radiation therapy after subtotal resection may prolong disease control.

Astrocytoma Astrocytomas are the most common intramedullary tumors in children, although they also occur in adults. They may occur at all levels, although more often in the cervical cord. The tumor may interfere with the CSF-containing central canal of the spinal cord, leading to a dilated central canal, referred to as *syringomyelia* (*syrinx*). Spinal astrocytomas are usually

low grade, but complete excision is rarely possible due to the nonencapsulated, infiltrative nature of the tumor. As a result, patients with astrocytomas fare worse overall than patients with ependymomas.

Other Tumors. Other types of rare tumors include high-grade astrocytomas, dermoids, epidermoids, teratomas, hemangiomas, hemangioblastomas, and metastases. Patients usually present with pain. Prognosis generally depends on preoperative function and the histologic characteristics of the lesion.

SPINE: BASIC CONCEPTS

The spine is a complex structure and is subject to an extensive array of pathologic processes, including degeneration, inflammation, infection, neoplasia, and trauma. Discussions of spine trauma, tumor, and infection are addressed separately in this chapter in the Infection—Spine, Spinal Tumors, and Spine Trauma sections. General concepts, common patterns of disease, and basic operative interventions are presented here.

The spine consists of a series of stacked vertebrae, intervening discs, and longitudinal ligaments. The vertebrae consist of the vertebral body anteriorly and the pedicles, articular facets, laminae, and spinous processes posteriorly. The intervertebral discs have two components. The tough, fibrous ring that runs around the outer diameter of the two adjacent vertebral bodies is known as the *annulus fibrosus*. The spongy material inside the ring of the annulus is known as the *nucleus pulposus*. The annulus and the nucleus provide a cushion between adjacent vertebral bodies, absorb forces transmitted to the spine, and allow some movement between the vertebral bodies. The ligaments stabilize the spine by limiting the motion of adjacent vertebrae.

Stability and neural compression are the two concepts critical to understanding the mechanics and pathologic processes affecting the spine.

Stability

The spinal column is the principal structural component of the axial spine, and it must bear significant loads. The vertebrae increase in size from the top to the bottom of the spine, correlating with the increased total loads that the more caudal elements must bear. The cervical spine is the most mobile. Cervical stability depends greatly on the integrity of the ligaments that run from level to level. The thoracic spine is the least mobile, due to the stabilizing effect of the rib cage. The lumbar spine has relatively massive vertebrae, supports heavy loads, and has intermediate mobility. The sacral spine is fused together and has no intrinsic mobility. The load borne by the lumbar spine is transmitted to the sacrum, and then the pelvis through the sacroiliac joints. The coccyx is the most inferior segment of the spine and has no significant contribution to load bearing or mobility.

A stable spine is one that can bear normally experienced forces resulting from body mass, movement, and muscle contraction, while maintaining normal structure and alignment. An unstable spine will shift or sublux under these forces. The determinants of spinal stability vary throughout the cervical, thoracic, and lumbar portions. In elementary form, stability depends on the structural integrity of the hard, bony elements of the vertebral column, as well as the tensile integrity and security of the supporting ligamentous attachments. Plain X-rays and CT scans are sensitive for detecting bony defects such as fractures or subluxation, while MRI better detects disruptions of the soft tissues, including ligaments and intervertebral discs. Specific

patterns of abnormalities seen on imaging studies may suggest or diagnose spinal instability.

A common form of nontraumatic spinal instability is lumbar spondylolisthesis, which is typically a forward slippage of a lumbar vertebra relative to the lower vertebra on which it rests. This results from congenital or degenerative disruption of the pars interarticularis, the critical bridge of bone that spans adjacent facet joints. In the setting of a pars defect, there is no solid bony connection between the adjacent vertebrae. The spine is unstable and anterior listhesis (slippage) may result. Patients typically present with severe low back pain that is exacerbated with movement and load bearing (mechanical low back pain). Radiculopathy in this setting indicates neuroforaminal compression. Figure 42-26 demonstrates an L4 and L5 spondylolisthesis.

Neural Compression

Besides providing a stable, central element of the body's support structure, the spine also protects the spinal cord and nerve roots as they pass through the neural foramina to form the peripheral nervous system. In a healthy spine, the spinal cord and nerve roots are suspended in CSF, free of mechanical compression. Pathologic processes that can lead to CSF space impingement and neural compression include: hypertrophic degenerative changes in the intervertebral discs and facet joints, expansion of epidural masses such as tumors or abscesses, and subluxation (i.e., slippage) of adjacent vertebral bodies. Subluxation may be due to trauma that exceeds the spine's load-bearing capabilities and leads to structural failure, or chronic structural degradation by degenerative disease, infection, or tumor. Subluxation

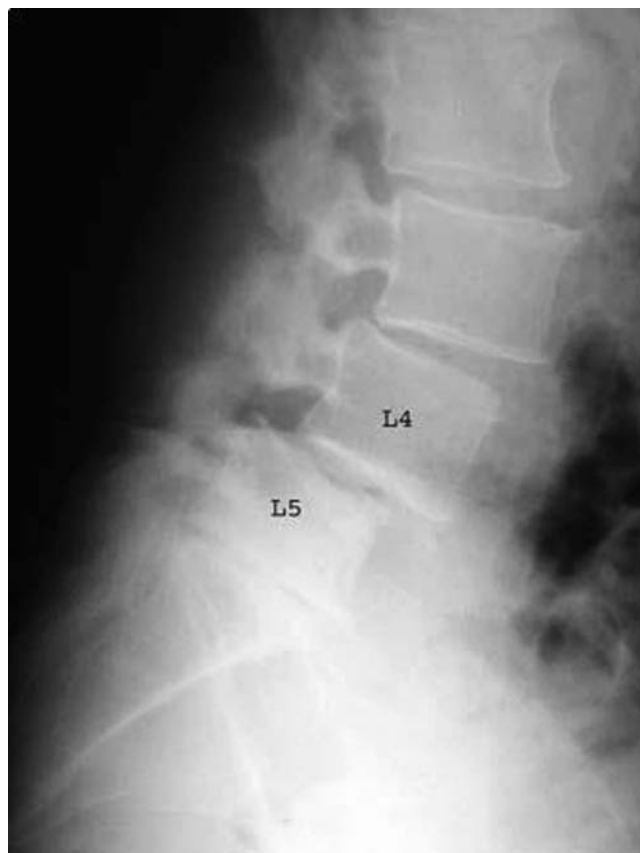


Figure 42-26. Lateral lumbar spine X-ray demonstrates a 25% anterior slippage of L4 on L5 due to a defect in the L4 pars interarticularis. This is called *spondylolisthesis*.

reduces the cross-sectional area of the central canal and the neural foramina (see Fig. 42-10B). Reduced central canal area can lead to myelopathy. Reduced neural foramina area can lead to radiculopathy.

Myelopathy. Compression of the spinal cord can cause disturbance of function known as *myelopathy*. This dysfunction may be secondary to the direct effects of compression, cord ischemia due to reduced perfusion, or pathologic changes due to repeated cord trauma. These mechanisms lead to demyelination of the corticospinal tracts, which are long descending motor tracts. Corticospinal tract damage leads to upper motor neuron signs and symptoms, including hyperreflexia, spasticity, and weakness. These mechanisms also cause damage to the dorsal columns, which carry ascending proprioception, vibration, and two-point discrimination information. Loss of proprioception makes fine motor tasks and ambulation difficult.

Radiculopathy. Compression of the nerve roots causes disturbance of root function, known as *radiculopathy*. Characteristic features of radiculopathy include lower motor neuron signs and symptoms (hyporeflexia, atrophy, and weakness) and sensory disturbances such as numbness or tingling sensations (paresthesias), burning sensations (dysesthesias), and shooting (radicular) pain. Myelopathy and radiculopathy often present together in diseases that involve the central canal and the neural foramina. This combination can lead to lower motor neuron dysfunction at the level of disease, and upper motor neuron dysfunction below that level.

Patterns of Disease

Cervical Radiculopathy. The cervical nerve roots exit the central canal above the pedicle of the same-numbered vertebra and at the level of the higher adjacent intervertebral disc. For example, the C6 nerve root passes above the C6 pedicle at the level of the C5–C6 discs. The cervical nerve roots may be compressed acutely by disc herniation, or chronically by hypertrophic degenerative changes of the discs, facets, and ligaments. Table 42-6 summarizes the effects of various disc herniations. Most patients with acute disc herniations will improve without surgery. NSAIDs or cervical traction may help alleviate symptoms. Patients whose symptoms do not resolve or who have significant weakness should undergo decompressive surgery. The two main options for nerve root decompression are anterior cervical discectomy and fusion (ACDF) and posterior cervical foraminotomy (keyhole foraminotomy). ACDF allows more direct access to and removal of the pathology (anterior to the nerve root). However, the procedure requires fusion because discectomy causes a collapse of the interbody space and instability will likely occur. Figure 42-27 demonstrates a

C6–C7 ACDF with the typical interposed graft and plating system. Keyhole foraminotomy allows for decompression without requiring fusion, but it is less effective for removing centrally located canal pathology.

Cervical Spondylotic Myelopathy. The term *spondylosis* refers to diffuse degenerative and hypertrophic changes of the discs, intervertebral joints, and ligaments, which collectively result in spinal stenosis. Spinal cord dysfunction (myelopathy) due to cord compression from cervical spinal degenerative disease is therefore referred to as *cervical spondylotic myelopathy* (CSM). Classically CSM presents with spasticity and hyperreflexia due to corticospinal tract dysfunction, upper extremity weakness and atrophy from degeneration of the motor neurons in the anterior horns of the spinal gray matter, and loss of lower extremity proprioception due to dorsal column injury. Figure 42-28 demonstrates typical findings. Some patients complain of difficulty buttoning shirts, using utensils, and ambulating. Spondylosis is usually diffuse, so the usual treatment for CSM is multilevel (usually C3–C7) cervical laminectomy, although patients with disease localized over one to three levels may be candidates for anterior decompression and fusion. Figure 42-29 demonstrates the postoperative appearance of a vertebral corpectomy and fusion for CSM. Thorough cervical laminectomy decompresses the cord posteriorly. Patients often have slow recovery due to the extensive chronic changes in the cervical cord and may benefit from rehabilitation programs. The other disease that classically presents with combined upper and lower motor neuron symptoms is amyotrophic lateral sclerosis (ALS). Care must be taken to avoid offering cervical laminectomy to a patient with undiagnosed ALS. Two findings help differentiate CSM from ALS: cranial nerve dysfunction such as dysphagia (not typically caused by cervical spine disease) and sensory disturbance (not found in ALS).

Thoracic Disc Herniation. Thoracic disc herniation accounts for <1% of herniated discs. A patient may present with radicular pain or sensorimotor changes in the lower extremities due to cord compression. A posterior approach via midline incision and laminectomy should be avoided because of the high incidence of cord injury from manipulation and retraction. Anterior approaches via thoracotomy minimize risk to the cord and allow excellent access to the disc. The radicular arteries running from the aorta to the thoracic cord should be spared, when possible, to avoid ischemia. Alternatively, a posterolateral approach is possible via resection of the rib head and facet joint. Finally, a transpedicular approach may be attempted for lateral disc herniations.³⁴

Lumbar Radiculopathy. Lumbar nerve roots exit the thecal sac, pass over the higher adjacent disc space, and exit the canal under the pedicle of the same-numbered vertebra. Therefore,

Table 42-6

Cervical disc herniations and symptoms by level

LEVEL	FREQUENCY (%)	ROOT INJURED	REFLEX	WEAKNESS	NUMBNESS
C4–C5	2	C5	—	Deltoid	Shoulder
C5–C6	19	C6	Biceps	Biceps brachii	Thumb
C6–C7	69	C7	Triceps	Wrist extensors (wrist drop)	Second and third digits
C7–T1	10	C8	—	Hand intrinsic	Fourth and fifth digits

Source: Adapted with permission from Greenberg MS. *Handbook of Neurosurgery*, 7th ed. New York: Thieme, 2010. Table 18–18, p 461.

**A****B**

Figure 42-27. **A.** Anteroposterior cervical spine X-ray showing the position of an anterior cervical plate used for stabilization after C6–C7 discectomy. Patient presented with right triceps weakness and dysesthesias in the right fifth digit. Magnetic resonance imaging revealed a right paracentral C6–C7 herniated disc compressing the exiting C7 nerve root. **B.** Lateral cervical spine X-ray of the same patient clearly demonstrates the position of the plate and screws. The allograft bone spacer placed in the drilled-out disc space is also apparent.



Figure 42-28. T2-weighted sagittal magnetic resonance imaging of the cervical spine showing multilevel degenerative changes causing spinal stenosis that is worst at C5–C6. Note the bright signal within the cord at that level, consistent with myelopathy.



Figure 42-29. Lateral cervical spine X-ray status post C5 corpectomy for cervical spondylotic myelopathy. This involves removal of the C4–C5 disc, C5 vertebral body, and C5–C6 disc, decompressing at two levels. A bone strut is visible bridging C4 to C6. The plate and screws stabilize the segments.

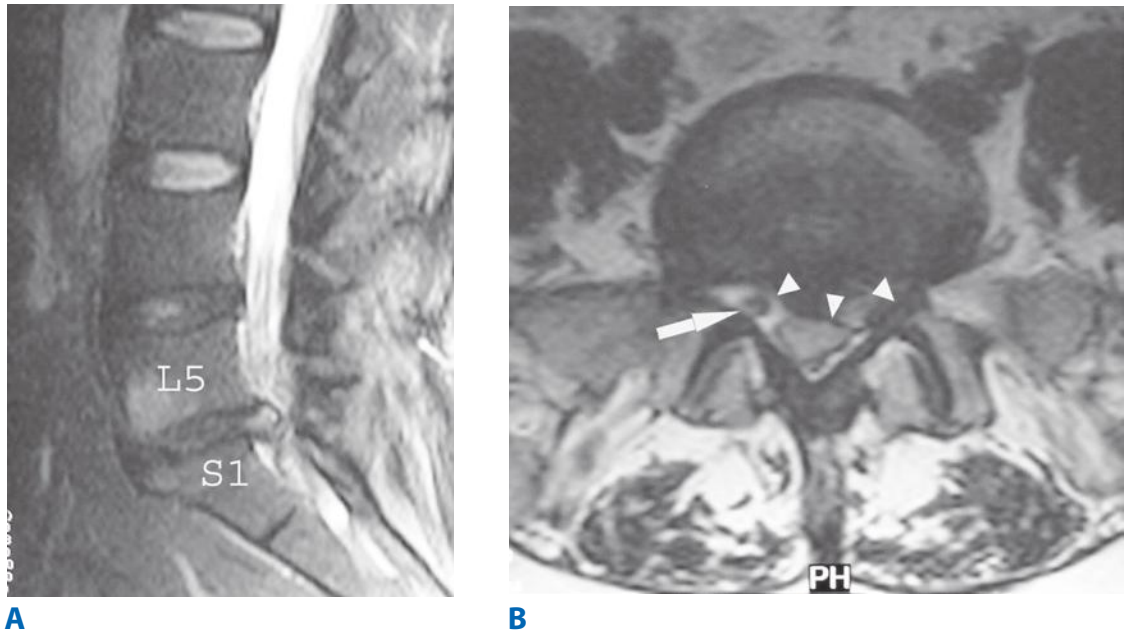


Figure 42-30. **A.** T2-weighted sagittal magnetic resonance imaging shows an L5–S1 disc herniation causing significant canal compromise and displacement of nerve roots. **B.** T2-weighted axial magnetic resonance imaging of the same patient shows the large left paracentral disc herniation at L5–S1. Arrowheads delineate the extent of the herniation. The arrow indicates the right S1 nerve root passing through free of compression. The left S1 nerve root is under severe compression and is not seen.

the L5 nerve root passes over the L4–L5 disc space and exits under the L5 pedicle (Fig. 42-30). Lumbar discs may herniate with or without a history of trauma or straining. Normally they cause lancinating (radicular) pain down the leg (Table 42-7). Most acute herniated lumbar discs improve symptomatically without surgery. Surgery is indicated for symptoms persisting more than 6 to 8 weeks, progressive motor deficit (e.g., foot drop), or for patients with incapacitating pain not manageable with analgesics.

Discectomy is performed using a midline incision, partial removal of the overlying laminae (hemilaminectomy or laminotomy), identification of the thecal sac and nerve root, and extraction of disc fragments. Free-floating disc fragments may be found. Often, however, the herniated disc material is still contained within the annulus, requiring incision of the posterior longitudinal ligament and curettage of the disc space. After lumbar discectomy, approximately two-thirds of patients will have complete relief of pain, and up to 85% will have significant improvement.

Neurogenic Claudication. Neurogenic claudication is characterized by low back and leg pain that occurs while walking and is relieved by stopping, leaning forward, or sitting. It is normally caused by degenerative lumbar stenosis causing

compression of the cauda equina. Neurogenic claudication must be distinguished from vascular claudication, which tends to resolve quickly with cessation of walking. There is typically no need to change position, and the pain follows a stocking distribution rather than a dermatomal distribution. Pallor and coldness of the feet, and normal neurologic examination are also typical, though diabetic patients may present a challenge with microvascular neuropathy. Patients with neurogenic claudication have a slowly progressive course and may be surgical candidates when their pain interferes with their lifestyle. The usual surgery is an L3 to L5 lumbar laminectomy to decompress the nerve roots.

Cauda Equina Syndrome. Cauda equina syndrome is due to compression of the cauda equina and may result from massive disc herniation, EDH, epidural abscess, tumor, or subluxation from trauma. Patients with cauda equina compression often present with urinary retention, saddle anesthesia, or progressing leg weakness. Saddle anesthesia is numbness in the perineum, genitals, buttocks, and upper inner thighs. Patients with suspected cauda equina syndrome should undergo immediate MRI of the lumbar spine to evaluate for a surgical lesion. Mass lesions should be removed urgently via laminectomy to preserve sphincter function and ambulation.

Table 42-7					
Lumbar disc herniations and symptoms by level					
LEVEL	FREQUENCY (%)	ROOT INJURED	REFLEX	WEAKNESS	NUMBNESS
L3–L4	5	L4	Patellar	Quadriceps	Anterior thigh
L4–L5	45	L5	—	Tibialis anterior (foot drop)	Great toe
L5–S1	50	S1	Achilles	Gastrocnemius	Lateral foot

Source: Adapted with permission from Greenberg MS. *Handbook of Neurosurgery*, 7th ed. New York: Thieme, 2010. Table 18–13, p 445.

Spine Fusion Surgery

Fusion surgery is often required for patients with spinal instability resulting from disease, surgical intervention, or both. Fusion procedures lock adjacent vertebrae together. Fusion occurs when the body forms a solid mass of bone incorporating the adjacent vertebrae, eliminating normal intervertebral movement. Stabilization and immobilization promote bony fusion. Internal instrumentation and external orthoses are often used to stabilize and immobilize the fused spinal segments.

Spinal Instrumentation

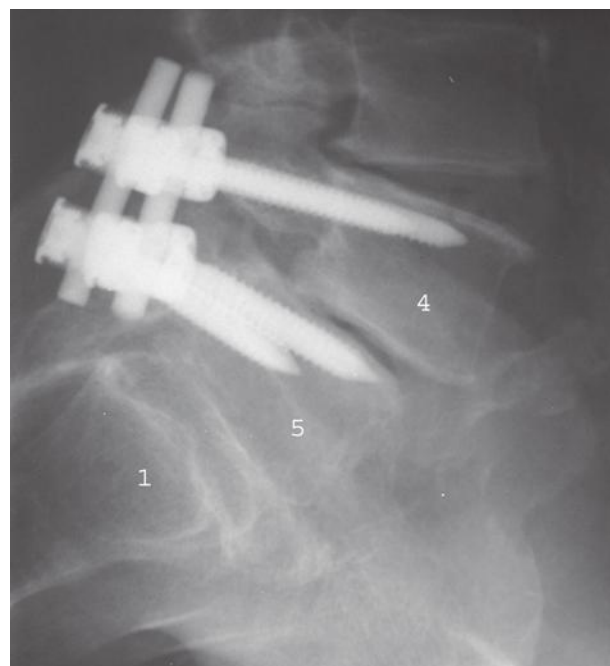
Internal fixation devices for spinal segmental immobilization have been developed for all levels of the spine. Most

6▶ spinal instrumentation constructs have two elements. The first element is a device that solidly attaches to the vertebral bodies. Options include wires wrapped around laminae or spinous processes, hooks placed under the lamina or around the pedicles, or screws placed in the pedicles or the vertebral bodies. The second element is a device that traverses vertebral segments. Options include rods and plates that lock directly to the wires, hooks, or screws at each vertebral level. Spinal instrumentation devices are available for anterior and posterior fusion in the cervical, thoracic, and lumbar regions. Most modern spinal instrumentation devices are made of titanium to minimize problems with future MRI scanning (Fig. 42-31). All spinal instrumentation constructs will eventually fail by loosening or breaking if bony fusion does not occur.

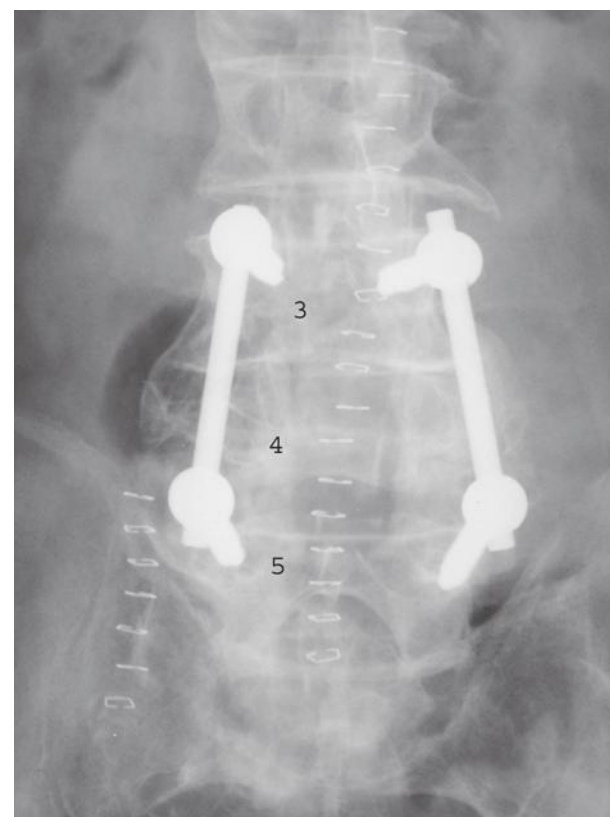
Arthrodesis

Arthrodesis refers to the obliteration of motion or instability by incorporating the relevant components into a solid mass of bone. Arthrodesis must occur in any fused segment to have long-term stability. Failure of arthrodesis results in failed fusion, often in the form of a fibrous nonunion. The rates of successful fusion are higher in the cervical spine than the lumbar spine. Arthrodesis requires ingrowth of new bone formed by the patient's osteoblasts across the unstable defect. Inserting graft material, such as autograft or allograft, into the defect provides a bridge for osteoblasts and promotes fusion. The term *autograft* refers to the patient's own bone, often harvested from the iliac crest. Iliac crest bone graft is a source of both cortical and cancellous bone. Cortical bone provides structural support, while cancellous bone provides a matrix for bony ingrowth. The term *allograft* refers to sterilized bone from human tissue banks. Allografts also may be cortical, cancellous, or both. Allograft lacks the array of osteoinductive endogenous compounds intrinsic to autograft, although supplemental products such as demineralized bone matrix paste can be added to encourage new bone formation. Other techniques for increasing the rates of successful fusion are being developed, including the integration of osteoinductive bone morphogenetic proteins, known as *BMPs*, into the fusion constructs.

Dynamic stabilization refers to the creation of spinal stability without achieving a bony fusion. The concept applies to both cervical and lumbar motion segments. Artificial lumbar and cervical disc replacement therapies are recent developments in degenerative spine disease that address this concept. However, their use is limited to very select cases. Another motion preservation technique that may hold promise is segmental "soft" stabilization.³⁵ In



A



B

Figure 42-31. **A.** Lateral lumbar spine X-ray showing pedicle screws and connecting rods used to stabilize L4 with respect to L5. This instrumentation was placed as part of a fusion operation to stabilize progressive L4-L5 spondylolisthesis with intractable low back pain. **B.** Anteroposterior lumbar spine X-ray showing L3 to L5 instrumentation with pedicle screws and connecting rods. The patient had previously sustained an L4 burst fracture. Note the significant loss of height of the L4 body compared to adjacent levels. The small row of staples to the right delineates the incision over the iliac crest used to harvest cancellous bone as a nonstructural osteoinductive autograft fusion designed to induce formation of a solid bone bridge from L3 to L5 (arthrodesis).

cases of degenerative spondylolisthesis, such systems in the lumbar spine allow for decompressive laminectomy without increasing slippage. In theory, adjacent level facets and discs are spared the stresses of a neighboring bony fusion moment arm.

PERIPHERAL NERVE

Common pathologic processes that compromise function of the peripheral nervous system include mechanical compression, ischemia, inflammation, and neoplasia.

Peripheral Nerve Tumors

Most peripheral nerve tumors are benign and grow slowly. Significant pain increases the likelihood that the patient has a malignant tumor. Treatment for peripheral nerve tumors is surgical resection to establish diagnosis and evaluate for signs of malignancy. These tumors have various degrees of involvement with the parent nerve. Some can be resected with minimal or no damage to the nerve. Tumors that grow within the nerve often contain functioning fascicles. Total excision of these tumors requires sacrifice of the parent nerve. The choice of subtotal resection, nerve preservation, and observation, vs. total resection with nerve sacrifice depends on tumor histology and the function of the parent nerve.

Schwannoma. Schwannomas are the most common peripheral nerve tumors, also referred to as *neurilemmomas* or *neurinomas*. Most occur in the third decade of life. These benign tumors arise from Schwann cells, which form myelin in peripheral nerves. The most characteristic presentation is a mass lesion with point tenderness and shooting pains on direct palpation. Spontaneous or continuous pain suggests malignancy. Schwannomas tend to grow slowly and eccentrically on parent nerves. The eccentric location and discrete encapsulated nature of these tumors often allow total resection without significant damage to the parent nerve. Subtotal resection and observation is reasonable for schwannomas entwined in important nerves, as the incidence of malignant transformation is extremely low.

Neurofibroma. Neurofibromas arise within the nerve and tend to be fusiform masses, unlike schwannomas, which tend to grow out of the nerve. Neurofibromas often present as a mass that is tender to palpation. They usually lack the shooting pains characteristic of schwannomas. Neurofibromas are often difficult to resect completely without sacrifice of the parent nerve. Neurofibromas have a higher incidence of malignant transformation; therefore, patients with known residual tumors require close observation. Patients with NF1 often have multiple neurofibromas. These patients should be offered resection for symptomatic tumors. Risk of malignant degeneration is up to 10%. Malignant neurofibromas have the histologic characteristics of sarcoma.

Malignant Nerve Sheath Tumors. Malignant nerve sheath tumors include solitary sarcomas, degenerated neurofibromas, and neuroepitheliomas. Patients with malignant peripheral nerve tumors typically complain of constant pain, rather than pain only on palpation, and are more likely to have motor and sensory deficits in the distribution of the parent nerve. Treatment for these tumors is radical excision. This often requires sacrifice of the parent nerve. Invasion of nearby soft tissues may

occur and necessitate wide resection or amputation in an attempt to prevent systemic metastasis.

Entrapment Neuropathies

Entrapment neuropathy presents as neurologic dysfunction in nerves passing through a pathologically small, fixed space. Nerve dysfunction may result directly from chronic, repetitive pressure on the nerve, or from ischemic damage due to impaired perfusion.³⁶ Entrapment causing dysfunction of nerve signaling may be associated with numbness, paresthesias, weakness, or muscle atrophy. The two most common sites of entrapment neuropathy are the ulnar nerve at the medial aspect of the elbow and the median nerve at the wrist. Usually EMG/NCS demonstrate slowing across the entrapped segment of nerve. Mechanical peripheral nerve disorders resulting from trauma (brachial plexus disruption, radial nerve damage from humerus fractures, and common peroneal nerve crush injuries) are discussed in the section on Trauma.

Ulnar Neuropathy. The ulnar nerve has contributions from the C7, C8, and T1 nerve roots, arises from the medial cord of the brachial plexus, and supplies most of the intrinsic hand muscles (interossei and third and fourth lumbricals), and sensation to the fourth and fifth digits. It passes posteriorly to the medial epicondyle at the elbow in the condylar groove. This segment is superficial and subject to external compression and repetitive minor impacts. Patients with ulnar entrapment at the elbow present with numbness and tingling in the medial palm, as well as the fourth and fifth digits. Motor deficits include weakness and wasting of the intrinsic hand muscles. Treatment for symptomatic ulnar entrapment neuropathy is surgical exploration and incision of the fibrous aponeurotic arch that overlies the nerve. A 6-cm curvilinear incision centered between the medial epicondyle and the olecranon allows exploration of up to 10 cm of nerve and lysis of compressive tissues.

Carpal Tunnel Syndrome. The median nerve has contributions from the C5 to T1 nerve roots, arises from the medial and lateral cords of the brachial plexus, and supplies the muscles of wrist and finger flexion and sensation to the palmar aspect of the first, second, and third digits. The median nerve passes through the carpal tunnel in the wrist, lying superficial to the four deep and four superficial flexor tendons. The transverse carpal ligament is a tough, fibrous band that forms the roof of the carpal tunnel. The ligament attaches to the pisiform and hamate medially and the trapezium and scaphoid laterally. Patients complain of numbness and tingling in the supplied digits, clumsiness, and worsening with sleep or repetitive wrist movement. Patients may notice wasting of the thenar eminence. Treatment for symptomatic carpal tunnel syndrome unresponsive to splinting, analgesics, and rest is surgical division of the flexor retinaculum. This often provides prompt relief of pain symptoms and slow recovery of numbness and strength.

Autoimmune and Inflammatory Disorders

These are not surgical diseases, but they merit brief mention as they are included in the differential diagnosis for new-onset weakness. Their characteristic presentations help distinguish them from weakness due to structural lesions.

Guillain-Barré Syndrome. Guillain-Barré syndrome is an acute inflammatory demyelinating polyradiculopathy often occurring after viral infection, surgery, inoculations, or

mycoplasma infections. Patients classically present with weakness ascending from the legs to the body, arms, and even cranial nerves. Symptoms usually progress over 2 to 4 weeks and then resolve. Care is supportive. Respiratory weakness may require ventilatory support.

Myasthenia Gravis. Myasthenia gravis is an autoimmune process in which antibodies form to the acetylcholine receptors of muscles, leading to fluctuating weakness. Most patients have either thymic hyperplasia or thymoma. The most common symptoms are diplopia, ptosis, dysarthria, and dysphagia. More severe cases have limb or respiratory involvement. Weakness worsens with repetitive movement. Treatment is with acetylcholinesterase inhibitors and possible thymectomy.

Eaton-Lambert Syndrome. Eaton-Lambert syndrome is an autoimmune process with antibodies to the presynaptic calcium channels. This is a paraneoplastic syndrome most commonly associated with oat cell carcinoma. Patients have weakness of proximal limb muscles that improves with repetitive movement. This diagnosis must prompt oncologic evaluation.

INFECTION

CNS infections of interest to neurosurgeons include those that cause focal neurologic deficit due to mass effect, require surgical aspiration or drainage because antibiotic therapy alone is insufficient, cause mechanical instability of the spine, or occur after neurosurgical procedures.

Cranial

Osteomyelitis. The skull is highly vascular and resistant to infections. Osteomyelitis of the skull may develop by contiguous spread from pyogenic sinus disease or from contamination by penetrating trauma. *Staphylococcus aureus* and *S. epidermidis* are the most frequent causative organisms. Patients usually present with redness, swelling, and pain. Contrast head CT aids diagnosis and shows the extent of involved bone, along with associated abscesses or empyema. Osteomyelitis treatment entails surgical debridement of involved bone followed by 2 to 4 months of antibiotics. Craniotomy wound infections are a special concern because performing a craniotomy creates a desvascularized free bone flap susceptible to infection and not penetrated by antibiotics. These wounds must be débrided and the bone flaps removed and discarded. Subsequent care involves appropriate antibiotic therapy, observation for signs of recurrent infection off antibiotics, and return to the OR for titanium or methylmethacrylate cranioplasty 6 to 12 months later.

Subdural Empyema. Subdural empyema is a rapidly progressive pyogenic infection. The subdural space lacks significant barriers to the spread of the infection, such as compartmentalization or septations. Subdural empyemas usually occur over the cerebral convexities. Potential infectious sources include sinus disease, penetrating trauma, and otitis. Streptococci and staphylococci are the most frequent sources. Presenting symptoms include fever, headache, neck stiffness, seizures, or focal neurologic deficit. Neurologic deficit results from inflammation of cortical blood vessels, leading to thrombosis and stroke. The most common deficit is contralateral hemiparesis. Patients with suggestive symptoms should undergo rapid contrast CT scan. LP frequently fails to yield the offending organism and risks

herniation due to mass effect. Typical treatment is wide hemi-craniectomy, dural opening, and lavage. The pus may be thick or septated, making burr hole drainage or small craniotomy insufficient. Patients then require 1 to 2 months of antibiotics. Subdural empyema has 10% to 20% mortality risk and common chronic sequelae, including development of a seizure disorder and residual hemiparesis. However, many patients do make a good recovery.

Brain Abscess. Brain abscess is encapsulated infection within the brain parenchyma. It may spread hematogenously in patients with endocarditis or intracardiac or intrapulmonary right-to-left shunts, by migration from the sinuses or ear, or via direct seeding by penetrating trauma. Disorganized cerebritis often precedes formation of the organized, walled-off abscess. Patients may present with nonspecific symptoms such as headache, nausea, or lethargy, or with focal neurologic deficit such as hemiparesis. Alternatively, patients may present in extremis if the abscess ruptures into the ventricular system. Abscesses appear as well-demarcated, ring-enhancing, thin-walled lesions on CT scan and MRI, and often have associated edema and mass effect. Patients require antibiotic therapy after needle aspiration or surgical evacuation. Antibiotic therapy without surgical evacuation may be considered for patients with small, multiple, or critically located abscesses. Abscesses that are large, cause mass effect, decreased mental status, or that fail to decrease in size after 1 week of antibiotics, should be evacuated. Nonsurgical management still requires aspiration or biopsy specimen for organism culture and sensitivities. Blood and CSF cultures rarely give definitive diagnosis. Removal of an encapsulated abscess significantly shortens the length of antibiotic therapy required to eliminate all organisms. Common chronic sequelae after successful treatment include seizures or focal neurologic deficit.

Spine

Pyogenic Vertebral Osteomyelitis. Pyogenic vertebral osteomyelitis is a destructive bacterial infection of the vertebrae, usually of the vertebral body. Vertebral osteomyelitis frequently results from hematogenous spread of distant disease, but may occur as an extension of adjacent disease, such as psoas abscess or perinephric abscess. *S. aureus* and *Enterobacter* spp. are the most frequent etiologic organisms. Patients usually present with fever and back pain. Diabetics, IV drug abusers, and dialysis patients have increased incidence of vertebral osteomyelitis. Epidural extension may lead to compression of the spinal cord or nerve roots with resultant neurologic deficit. Osteomyelitis presents a lytic picture on imaging and must be distinguished from neoplastic disease. Adjacent intervertebral disc involvement occurs frequently with pyogenic osteomyelitis, but rarely with neoplasia. Plain films and CT help assess the extent of bony destruction or deformity such as kyphosis. MRI shows adjacent soft tissue or epidural disease. Most cases can be treated successfully with antibiotics alone, although the organism must be isolated to steer antibiotic choice. Blood cultures may be positive. Surgical intervention may be required for debridement when antibiotics alone fail, or for stabilization and fusion in the setting of instability and deformity.

Tuberculous Vertebral Osteomyelitis. Tuberculous vertebral osteomyelitis, also known as *Pott's disease*, occurs most commonly in underdeveloped countries and in the immunocompromised.

Several features differentiate tuberculous osteomyelitis from bacterial osteomyelitis. The infection is indolent and symptoms often progress slowly over months. Tuberculosis rarely involves the intervertebral disc. The involved bodies may have sclerotic rather than lytic changes. Multiple nonadjacent vertebrae may be involved. The upper lumbar and lower thoracic vertebrae are most commonly affected. Diagnosis requires documentation of acid-fast bacilli. Treatment involves long-term antimycobacterial drugs. Patients with spinal instability or neural compression from epidural inflammatory tissue should undergo debridement and fusion as needed.

Discitis. Primary infection of the intervertebral disc space, or discitis, is most commonly secondary to postoperative infections. Spontaneous discitis occurs more commonly in children. *S. aureus* and *S. epidermidis* account for most cases. The primary symptom is back pain. Other signs and symptoms include radicular pain, fevers, paraspinal muscle spasm, and localized tenderness to palpation. Many cases will resolve without antibiotics, which generally are given for positive blood or biopsy specimen cultures or persistent constitutional symptoms. Most patients will have spontaneous fusion across the involved disc and do not need debridement or fusion.

Epidural Abscess. Epidural abscesses may arise from or spread to the adjacent bone or disc, so distinguishing between vertebral osteomyelitis or discitis and a spinal epidural abscess may be difficult. The most common presenting signs and symptoms are back pain, fever, and tenderness to palpation of the spine. The most significant risk of epidural abscess is weakness progressing to paralysis due to spinal cord or nerve root damage. Cord and root damage may be due to direct compression or to inflammatory thrombosis resulting in venous infarction. *S. aureus* and *Streptococcus* spp. are the most common organisms. Methicillin-resistant *S. aureus* now constitutes a significant proportion of these infections, as high as 40%.³⁷ The source may be hematogenous spread, local extension, or operative contamination. MRI best demonstrates the epidural space and degree of neural compromise. Patients with spinal epidural abscess and neurologic compromise should undergo surgical debridement for decompression and diagnosis, followed by culture-directed antibiotic therapy. Relative contraindications to surgery include prohibitive comorbidities or total lack of neurologic function below the involved level. Patients with no neurologic deficits and an identified organism may be treated with antibiotics alone and very close observation. However, this management strategy remains somewhat controversial because these patients can undergo rapid and irreversible neurologic decline. Most epidural abscesses can be accessed via laminectomy without fusion. Collections predominantly anterior to the cervical or thoracic cord may require anterior approach and fusion.

FUNCTIONAL NEUROSURGERY

Epilepsy Surgery

Seizures result from uncontrolled neuronal electrical activity. Seizures may result from irritative lesions in the brain, such as tumors or hematomas, or from physiologic or structural abnormalities. Seizures may involve a part of the brain (focal) or the entire brain (generalized). Focal seizures may be associated with normal consciousness (simple) or decreased consciousness (complex). All generalized seizures cause loss of consciousness. Focal seizures may secondarily generalize. Patients with

multiple unprovoked seizures over time are considered to have epilepsy. The type of epilepsy depends on such factors as type of seizures, electroencephalographic (EEG) findings, associated syndromes, and identifiable etiologies. All patients with unexplained seizures (i.e., no obvious cause such as head trauma or alcohol withdrawal) require thorough neurologic evaluation, including imaging to evaluate for a mass lesion. Antiepileptic drugs (AEDs) form the first line of therapy for epilepsy, initially as monotherapy, then as combination therapy. Epilepsy patients who have failed satisfactory trials of several AED combination regimens may be candidates for surgical intervention. Lack of seizure control or patient intolerance of the medications may constitute failure. Epilepsy surgery can decrease the frequency of seizures by resection of the electrical source of the seizures, or decrease the severity of seizures by disconnecting white matter tracts through which the abnormal electrical activity spreads. Four types of epilepsy surgery are discussed in sections that follow. Epilepsy surgery appears to be extremely underused, given the relatively low risk of the procedures, and the crippling social and economic effects of uncontrolled or partially controlled epilepsy.³⁸ Patients with symptoms, imaging abnormalities, and EEG analysis compatible with a specific seizure focus are most likely to have good results from epilepsy surgery.

Anterior Temporal Lobectomy. Medial temporal lobe structural abnormalities can lead to complex partial seizures (CPS). Many patients with CPS have poor seizure control on medications. Patients with CPS may have significant reduction in seizure frequency or cessation of seizures after resection of the anterior temporal lobe. The amygdala and the head of the hippocampus are removed as part of the lobectomy. Resection may be taken back approximately 4.5 cm from the temporal tip in the language-dominant hemisphere, and 6 cm from the temporal tip in the language nondominant hemisphere, with low risk of significant neurologic deficits.³⁹ The two main risks of anterior temporal lobectomy are memory impairment and visual loss. Removal of the hippocampus in a patient with an atrophied or nonfunctional contralateral hippocampus causes a global memory deficit. Interruption of the optic radiations, which carry visual signals from the contralateral superior visual quadrants of both eyes, causes a contralateral superior quadrantanopia, known as a *pie in the sky* field cut.

Corpus Callosotomy. Patients with generalized seizures, atonic seizures associated with drop attacks, or absence seizures, who are found to have bilaterally coordinated pathologic cortical discharges on EEG and who fail AED therapy, may be candidates for corpus callosotomy. The corpus callosum is a large white matter tract that connects the cerebral hemispheres. Loss of consciousness requires simultaneous seizure activity in both hemispheres. Focal or partial seizures may spread via the corpus callosum to the contralateral hemisphere, causing generalization and loss of consciousness. Division of the corpus callosum can interrupt this spread. Patients may have decreased numbers of seizures and/or fewer episodes of lost consciousness. Usually only the anterior half or two-thirds of the corpus callosum is divided, as more extensive division increases the risk of disconnection syndrome. Patients with disconnection syndrome are unable to match objects in the opposite visual hemifields, to identify objects held in one hand with the other hemifield, and to write with the left hand or name objects held in the left hand (in left hemisphere-dominant patients).

Hemispherectomy. Children with intractable epilepsy, structural anomalies in one hemisphere, and contralateral hemiplegia, may have improved seizure control after resection of the hemisphere (anatomic hemispherectomy) or disruption of all connections to the hemisphere (functional hemispherectomy). Functional hemispherectomy often is preferred over anatomic hemispherectomy because of the high incidence of complications such as hematoma formation and ventriculoperitoneal shunt dependence associated with the latter.

Vagus Nerve Stimulation. Neuromodulatory treatments like vagus nerve stimulation (VNS), approved by the FDA in 1997, are less invasive and offer some titratability in addition to reversibility unlike the resective surgical options previously described. Since first reported in 1985, VNS has proven to be efficacious in certain patient populations for several disorders such as treatment-resistant major depressive disorder, bipolar disorder, and epilepsy. In VNS, a pulse generator is placed under the skin in the chest and is connected to the vagus nerve by an electrical lead. Chronic, intermittent VNS has been proven to be an effective option for patients suffering from medically refractory seizures who are not candidates for surgical resection. Although only a small minority of patients will be entirely seizure-free, three blinded, randomized-controlled trials have examined VNS, and demonstrated significant clinical improvement compared to sham.⁴⁰⁻⁴² Generally VNS is well-tolerated and safe, as device implantation is associated with a low rate of perioperative complications. Additionally, the majority of side effects are stimulation-dependent and thus, reversible. For the most part, VNS is limited in its application because it can only exert its effects by altering neural activity via the vagus nerve. Procedures with brain region-specificity are being investigated.

Deep Brain Stimulation

The following summary of deep brain stimulation (DBS) will include a review of the current U.S. Food and Drug Administration (FDA)-approved indications, as well the expanding applications of this therapy, currently being investigated preclinically and in clinical trials. While the mechanism of action of DBS continues to elude our understanding, it is well-established that administering electrical stimulation to a nucleus in the brain known to be involved in a given disease can disrupt the pathologic signals emanating to or from this brain region. A fine electrical lead is placed in a deep brain nucleus and connected to pulse generators placed in the chest in a manner similar to cardiac pacemakers. Connector wires travel from the generators in the subcutaneous space up the neck and in the subgaleal space in the head, to connect the pulse generators to the electrical leads. Proper lead placement is accomplished with stereotactic guidance. A frame is rigidly fixed to the patient's head, and an MRI is obtained with the frame in place. Calculation of the coordinates of the millimeter-sized deep brain nuclei is performed in relation to the three-dimensional space defined by the fixed frame, allowing for accurate targeting of the nucleus (Fig. 42-32). Postoperatively, the pulse generators can be interrogated and adjusted with hand-held, transcutaneous, noninvasive devices as needed for symptom control.

Essential Tremor. Essential tremor is the most common movement disorder in the western world and is characterized by action tremor (4–8 Hz rhythmic oscillations) of the hands, forearms, head, and voice. Essential tremor often starts in the third or fourth decade of life, and increases in frequency and



Figure 42-32. Fast spin echo coronal magnetic resonance imaging demonstrating position of deep brain stimulator leads in the subthalamic nuclei bilaterally. The electrodes appear thick and wavy due to magnetic susceptibility artifact.

amplitude with age. Beta blockers can decrease symptoms, but patients with poor medical control and significant functional impairment significantly benefit from placement of a deep brain stimulator in the contralateral ventralis intermediate nucleus of the thalamus. In properly selected patients, DBS of this region of the thalamus appears to provide robust and durable symptom control.^{43,44}

Parkinson's Disease. Parkinson's disease is a progressive disorder characterized by rigidity, bradykinesia, and resting tremor, due to loss of dopamine-secreting neurons in the substantia nigra. Dopaminergic agents such as levodopa/carbidopa and anticholinergic agents such as amantadine and selegiline form the basis of medical therapy. Patients with poor medical control or significant drug side effects may benefit significantly from placement of bilateral deep brain stimulators in the subthalamic nuclei. Although the globus pallidus interna has also been a widely targeted area, the subthalamic nuclei is now the most accepted target in deep brain stimulation for Parkinson's disease.⁴⁵ Deep brain stimulation provides durable symptom relief with good postoperative neuropsychologic function in properly selected patients.⁴⁶

Recently, a large randomized controlled trial compared bilateral DBS ($n=121$) to best medical therapy in advanced Parkinson's disease ($n=134$).⁴⁷ The DBS group did significantly better in both motor function and quality of life. While adverse events were 3.8 times more likely in the DBS group, 99% of these events had resolved by 6 months. There was a 0.8% risk of death due to the procedure, and there was no difference in risk of adverse events when comparing older (≥ 70 years) to younger patients (< 70 years). Thus, the benefits of DBS over medical therapy are clear, especially when considering quality of life measures.

Another recent randomized controlled trial focused on defining the optimal targets for DBS in Parkinson's disease.⁴⁸ While the subthalamic nucleus (STN) and the globus pallidus interna (GPi) have been successfully targeted in the past, a direct comparison of the two was lacking. In this study, 299 subjects

were randomized to receive either bilateral STN or GPi stimulators and were evaluated for 2 years. The primary outcome was motor function, as assessed by part III of the Unified Parkinson's Disease Rating Scale (UPDRS). The study found no significant difference in motor improvement between target sites. However, a significant difference was found in a secondary outcome measuring depression. On the Beck Depression Inventory, the pallidal stimulation group improved slightly compared with the STN group, which actually worsened slightly. Nevertheless, the actual incidence of depressive episodes requiring prolonged or new hospitalization was 2.6% and 0.7% in GPi and STN, respectively, which was not significantly different. On the other hand, the STN group was found to require less adjunctive dopaminergic pharmacotherapy than the GPi group. In terms of overall severe adverse events, there was no difference between groups. The investigators concluded that both target sites are effective and that nonmotor factors such as psychiatric symptoms may be a consideration in DBS target selection.

Dystonia. The FDA humanitarian device exemption has been made for DBS for dystonia, but is limited to patients ≥ 7 years of age with primary dystonia, including generalized and/or segmental dystonia, hemidystonia, or cervical dystonia (torticollis). Dystonia is characterized by sustained muscle contractions that cause repetitive movements and involuntary postures. Cognitive function is typically spared, and pharmacological therapy is frequently inadequate. The positive impact of DBS on Parkinson's and essential tremor has led neurologists and neurosurgeons to direct their attention to DBS for treatment of idiopathic focal and generalized dystonia.

Although the pathophysiology of idiopathic dystonia is unclear, positron-emission tomography studies have shown disturbed glucose metabolism in the GPi, suggesting secondary pathologic activation of the motor cortex. Indeed, the GPi is currently considered the most efficacious target for dystonia, and controlled trials indicate approximately a 50% improvement in motor function and disability.⁴⁹ Since many patients undergoing surgery for dystonia are children and young adults, DBS is an attractive surgical option because it can be titrated, revised and reversed according to individual needs and growth patterns.

Obsessive-Compulsive Disorder. The safety and efficacy of DBS, as well as its titratability and reversibility, that have been demonstrated for the treatment of movement disorders in the 1990s and 2000s has spawned an increasing interest and awareness of the capabilities of nonlesional surgical treatments for diseases of the brain. An obvious outgrowth of DBS for movement disorders has been the treatment of medically refractory psychiatric disorders. Despite the dark history of frontal leucotomy procedures that dominated the early 20th century, nonlesional DBS for psychiatric disorders are now considered potential treatment strategies.

Functional neuroimaging has implicated certain brain regions in the pathogenesis of a variety of psychiatric disorders. The FDA has approved a humanitarian device exemption for DBS targeting the ventral capsule/ventral striatum for severe obsessive-compulsive disorder (OCD). Recent case reports and pilot studies have reported remission in patients suffering from refractory OCD following DBS. A pilot study using a blinded, staggered-onset design found that four (66.7%) of six patients met a stringent criterion as "responders" ($\geq 35\%$ improvement), according to the Yale-Brown Obsessive Compulsive Scale after 12 months of stimulation.⁵⁰ In this study, patients did not improve during the sham phase. Adverse events were generally

mild and modifiable with setting changes, and stimulation interruption led to rapid yet reversible development of depressive symptoms in two cases. Thus, DBS has promise as a therapy of last resort for carefully selected cases of severe OCD.

Expanding Indications of Deep Brain Stimulation. There are multiple disorders, both psychiatric and neurologic, that have exhibited significant promise as potential indications for DBS in large-scale trials. Recently, there have been reports of significant improvements in refractory depression with DBS. Lozano and colleagues performed an open label study with extended follow-up on 20 patients targeting an area within the subcallosal cingulate gyrus (SCG) with bilateral DBS.⁵¹ At the last follow-up visit in this study (range: 3–6 years), the average response rate was 64%, according to the Hamilton Rating Scale for Depression. Of note, impairment in social functioning was improved, and no significant adverse events were reported. Because two patients died by suicide during depressive relapses, it remains unclear if DBS can only improve quality of life or significantly suppress relapses and extend life-span in this extremely delicate patient population. Of note, as seen in OCD, the ventral capsule/ventral striatum has also been targeted for depression, as well as the nucleus accumbens directly, which lies within the ventral striatum. Studies of DBS in this region report an approximate 40% to 60% response rate, and results from a recent, multicenter randomized controlled trial are pending.⁵²

DBS as a potential therapy for epilepsy targeting the anterior nucleus of the thalamus has been investigated in a multicenter, double-blind, randomized trial (SANTE).⁵³ In this trial, the group receiving DBS showed a 29% greater reduction in seizure frequency in relation to the sham group in the last month of the blinded phase. Complex partial and the "most severe" seizures were significantly reduced in the DBS-on group. After the blinded phase of the trial was complete, 54% of patients had a seizure reduction of at least 50%. Fourteen patients were seizure-free for at least 6 months; eight were seizure-free for at least one year, four for at least two years, and one patient for more than four years. Because of the modest benefit during the blinded phase of this trial, FDA-approval has yet to be granted to DBS for epilepsy targeting the thalamus in the United States, though approval has been given in Europe and Canada.

The region-specific, neuromodulatory capabilities of DBS have inspired the open label use of this technique in many other neurologic and psychiatric disorders, including but not limited to Tourette syndrome, Huntington's disease, and Alzheimer disease. Preclinical studies of both substance abuse and obesity have also shown promise.^{54,55} The opportunity to model reward-seeking behaviors associated with these disorders in animals provides the ability to not only test safety, but also study mechanisms and inform the design of future clinical trials.

Trigeminal Neuralgia

Trigeminal neuralgia, also known as *tic douloureux*, is characterized by repetitive, unilateral, sharp, and lancinating pains in the distribution of, typically, the second, but sometimes third, branch of cranial nerve V, the trigeminal nerve. The patient may describe a "trigger point," an area on the face that elicits the pain when touched. A current leading etiologic hypothesis for trigeminal neuralgia is irritation and pulsatile compression of the root entry zone of the nerve by an artery in the posterior fossa, usually a loop of the superior cerebellar artery. The pain is excruciating and can be debilitating. Medical therapy, including carbamazepine and amitriptyline, may

reduce the frequency of events. Options for medically refractory cases include percutaneous injection of glycerol into the path of the nerve, peripheral transection of the nerve branches, SRS, and microvascular decompression (MVD).

MVD involves performing a small posterior fossa craniotomy on the side of the symptoms, retraction of the cerebellar hemisphere, and exploration of cranial nerve V. If an artery is found near the nerve, the vessel is freed of any adhesions and nonabsorbable material is placed between the nerve root and the artery. MVD remains the first definitive management option because SRS is associated with a substantial incidence of facial numbness.^{56,57}

STEREOTACTIC RADIOSURGERY

The term *stereotactic radiosurgery* (SRS) refers to techniques that allow delivery of high-dose radiation that conforms to the shape of the target and has rapid isodose fall-off, minimizing damage to adjacent neural structures. The two most common devices used for conformal SRS for intracranial lesions are the LINAC (linear accelerator) and the gamma knife. LINAC delivers a focused beam of X-ray radiation from a port that arcs part way around the patient's head. Linear accelerators are commonly used to provide fractionated radiation for lesions outside the CNS. They are found in most radiation oncology departments. After upgrades to the software and collimators, SRS can be performed with these existing units. The gamma knife delivers 201 focused beams of gamma radiation from cobalt sources through a specially designed colander-like helmet. Gamma knife units are used only for intracranial disease and cost up to \$5 million; thus, they are most appropriate in high patient-volume centers. There is ongoing debate in the literature regarding the two technologies.^{58–60} Both continue to evolve, allowing more precise and complex isodose conformation to complex lesions. Most lesions can be treated equally well with either technology. Lesions abutting the medulla or the spinal cord should not be treated with SRS, because these structures do not tolerate the radiation dose delivered to structures within millimeters of the target. Also, medullary or spinal cord compression can result from swelling of the lesion after the radiosurgery dose, resulting in devastating neurologic deficit.

Proton beam is an evolving SRS technology that may play a specialized role in treatment of lesions where posttarget exiting radiation limits photon-based therapies.⁶¹ For example, the physical properties of protons cause destruction upon entry and exit from tissue, which can be particularly harmful to skull-base or clival lesions such as chordoma, in which the exiting pathway travels through the brain stem. Proton beam therapy uses accelerated protons, which dissipate energy upon impact and do not cause additional exiting damage. Currently, there are very few centers using this technology.

CyberKnife is another radiosurgery system that has neurosurgical application. It is a frameless, robotic, LINAC-based system that allows for targeting of spinal neoplasms with higher resolution than conventional external beam radiotherapy.⁶² Using imaging tracking in real time, the CyberKnife is able to adjust to breathing artifact and patient movement. The application of this technology is rapidly growing.

Arteriovenous Malformations

SRS has been found to be an effective stand-alone therapy for AVMs up to 3 cm in diameter. SRS is best for lesions that are difficult to access surgically due to high likelihood of postoperative neurologic deficit. However, SRS is not effective

for lesions >3 cm. Effective obliteration and elimination of the risk of hemorrhage takes 2 to 3 years. Overall, there is an approximately 2% annual incidence of AVM hemorrhage,⁶³ although one study found a 50% decrease in hemorrhage rate during the latency period before angiographic obliteration.⁶⁴ Nonetheless, surgical excision remains the preferred therapeutic modality, while SRS is reserved for cases deemed very high-risk for surgery due to location or patient factors.⁶⁵ Some patients with large AVMs who undergo surgery will have unresectable residual lesions. In these patients, SRS may be used as an effective adjunctive therapy in these patients.

Vestibular Schwannomas

SRS has been introduced as a therapeutic alternative to microsurgical resection for vestibular schwannomas up to 2.5 cm in maximum diameter. SRS provides high rates of tumor growth arrest and possible reduction in size with low rates of facial nerve palsy. Patients with functional ipsilateral preprocedure hearing may be more likely to retain functional hearing postprocedure than with microsurgery. The limitations of SRS include inability to treat tumors >2.5 cm, the possibility of radiation-induced malignant transformation of these benign tumors, and lack of long-term follow-up. SRS centers are accumulating experience with these tumors and accumulating data on long-term results.^{66,67} The indications for microsurgery and SRS will continue to evolve. Either approach should be undertaken at a high-volume center, as studies show the patient outcomes improve with increased surgeon experience.⁶⁸

Intracranial Metastases

Patients with solitary or multiple intracranial metastases may be treated primarily with SRS.⁶⁹ Patients have improved survival after SRS compared to no treatment or WBRT, and similar survival to patients undergoing total surgical resection. Patients with lesions >3 cm in diameter or evidence of ICH should undergo surgical decompression rather than SRS. Some studies show improved survival with up to seven intracranial masses. Patients with multiple intracranial masses have almost zero long-term survival, and most will die of their intracranial disease. Patients with intracranial metastases live 3 to 6 months on average with medical care and WBRT. This can be extended to 9 to 16 months with SRS or surgery, depending on tumor type, age, and patient condition.⁷⁰

CONGENITAL AND DEVELOPMENTAL ANOMALIES

Dysraphism

Dysraphism describes defects of fusion of the neural tube involving the neural tube itself, or overlying bone or skin. Dysraphism may occur in the spine or head. Neural tube defects are among the most common congenital abnormalities. Prenatal vitamins, especially folic acid, reduce the incidence of neural tube defects.

Spina Bifida Occulta

Spina bifida occulta is congenital absence of posterior vertebral elements. The spinous process is always missing, the laminae may be missing to various degrees, but the underlying neural tissues are not involved. Spina bifida occulta is found in 25% of the general population, and is asymptomatic unless associated with other developmental abnormalities.

Spina Bifida with Myelomeningocele

Spina bifida with myelomeningocele describes the congenital absence of posterior vertebral elements with protrusion of the meninges through the defect, with underlying neural structural abnormalities. Common findings include weakness and atrophy of the lower extremities, gait disturbance, urinary incontinence, constipation, and deformities of the foot. Myelomeningoceles arising from the high lumbar cord usually cause total paralysis and incontinence, while those arising from the sacral cord may have only clawing of the foot and partial urinary function loss. Myelomeningocele patients often have hydrocephalus and a Chiari II malformation, an abnormal downward herniation of the cerebellum and brain stem through the foramen magnum. Patients with abnormal protrusion of meninges through the bony defect without abnormalities of the underlying neural tissue have a meningocele. Most of these patients are neurologically normal.

Encephalocele

Herniation of brain encased in meninges through the skull that forms an intracranial mass is referred to as *encephalocele*. Herniation of meninges without brain tissue is referred to as a *meningocele*. Most occur over the convexity of the skull. More rarely, the tissue protrudes through the skull base into the sinuses. Treatment involves excision of the herniated tissue and closure of the defect. Most patients with encephaloceles and meningoceles have impaired cognitive development. Patients with greater amounts of herniated neural tissue tend to have more severe cognitive deficits.

Craniosynostosis

Craniosynostosis is the abnormal early fusion of a cranial suture line with resultant restriction of skull growth in the affected area and compensatory bulging at the other sutures. Skull growth occurs at the cranial sutures for the first 2 years of life, at the end of which the skull has achieved >90% of its eventual adult size. Fusion of the sagittal suture, or sagittal synostosis, results in a boat-shaped head, known as *scaphocephaly*. Unilateral coronal synostosis results in ipsilateral forehead flattening and outward deviation of the orbit, known as *plagiocephaly*. The contralateral normal forehead appears to bulge by comparison. Bilateral coronal synostosis results in a broad, flattened forehead, known as *brachycephaly*, and is often associated with maxillary hypoplasia and proptosis. Unilateral or bilateral lambdoid synostosis results in flattening of the occiput. Occipital flattening can result from abnormal suture fusion (synostosis), or from physical remodeling of the skull caused by always placing the baby in the supine position for sleep (known as *positional plagiocephaly*). Placing the baby in the prone position or tilted onto the contralateral side may restore near-normal skull shape in most cases of lambdoid synostosis, avoiding surgery. Treatment for synostoses in general is surgical, involving resection of the fused suture, or more complex reconstructive techniques for severe or refractory cases.

Hydrocephalus

Excess CSF in the brain that results in enlarged ventricles is known as *hydrocephalus*. CSF flows from the ventricles to the subarachnoid space and is then absorbed into the venous blood through the arachnoid granulations. Hydrocephalus may be classified as communicating or obstructive (outlined in the next two sections), and congenital or acquired. Congenital lesions

associated with or causing hydrocephalus include stenosis of the cerebral aqueduct, Chiari malformation, myelomeningocele, and intrauterine infection. Acquired hydrocephalus may result from occlusion of arachnoid granulations by meningitis, germinal matrix hemorrhage, or SAH. CSF pathways may be occluded by adjacent tumors (Fig. 42-33).



A



B

Figure 42-33. **A.** Axial head computed tomography scan revealing dilated ventricular system. Note dilated atria of the lateral ventricles (arrowheads) and rounded third ventricle (arrow). The large size of the ventricles and lack of transependymal flow indicate a chronic process (contrast to Fig. 42-2). The patient had normal-pressure hydrocephalus and had improved ambulation after placement of a ventriculoperitoneal shunt. **B.** Higher cut from same scan showing ventricular catheter in place in the frontal horn of the right lateral ventricle.

Communicating Hydrocephalus. Obstruction at the level of the arachnoid granulations constitutes communicating hydrocephalus. This usually causes dilation of the lateral, third, and fourth ventricles equally. The most common causes in adults are meningitis and SAH. Hydrocephalus may be transient after SAH, with re-establishment of normal CSF absorption after the protein content of the CSF returns to normal and the granulations reopen.

Obstructive Hydrocephalus. Obstruction of CSF pathways is known as *obstructive hydrocephalus*. Ventricles proximal to the obstruction dilate, while those distal to the obstruction remain normal in size. Typical patterns include dilation of the lateral ventricles due to a colloid cyst occluding the foramen of Monro, dilation of the lateral and third ventricles due to a tectal (midbrain) glioma or pineal region tumor occluding the cerebral aqueduct, or dilation of the lateral and third ventricles with obliteration of the fourth ventricle by an intraventricular tumor of the fourth ventricle. Obstructive hydrocephalus may present precipitously and require urgent shunting to prevent herniation.

Chiari I Malformation

Chiari I malformation is the caudal displacement of the cerebellar tonsils below the foramen magnum. It may be seen as an incidental finding on MRI scans in asymptomatic patients. Symptomatic patients usually present with headache, neck pain, or symptoms of myelopathy, including numbness or weakness in the extremities. A syrinx may be associated, but the brain stem and lower cranial nerves are normal in Chiari I malformations. Chiari II malformations are more severe and involve caudal displacement of the lower brain stem and stretching of the lower cranial nerves. Symptomatic patients may be treated with suboccipital craniectomy to remove the posterior arch of the foramen magnum, along with removal of the posterior ring of C1. Removal of these bony structures relieves the compression of the cerebellar tonsils and cervicomedullary junction, and may allow re-establishment of normal CSF flow patterns. Figure 42-34 demonstrates typical MRI appearance of a Chiari I malformation.

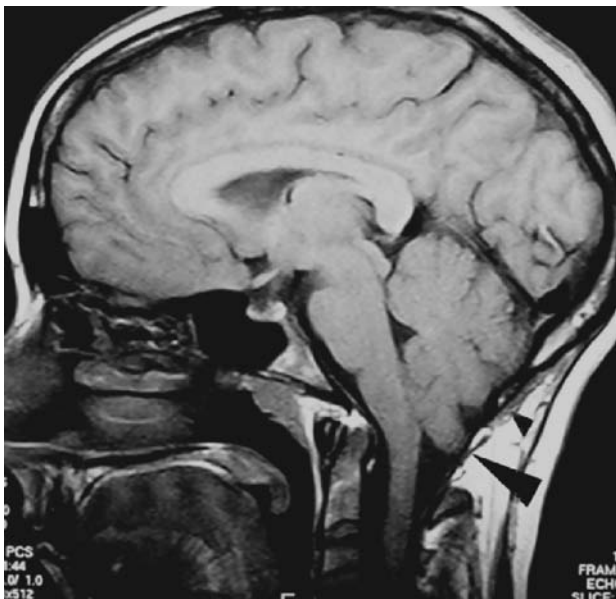


Figure 42-34. T1-weighted sagittal magnetic resonance imaging of a patient with a Chiari I malformation. The *large arrowhead* points to the cerebellar tonsils. The *small arrowhead* points to the posterior arch of the foramen magnum.

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chapter

Orthopedic Surgery

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Key Point

- 1▶ The main principle of internal fixation for fracture care (most commonly intramedullary nails or plate and screw fixation) is to create a stable construct that will allow the fracture to heal in proper alignment.
- 2▶ Often, in open fractures, definitive treatment of the fracture is delayed until the wound is sufficiently cleaned and healthy soft tissue is available to cover the fracture.
- 3▶ When compartment syndrome is suspected, emergent fasciotomy must be performed in which the overlying tight fascia is released through long incisions. These must be done as soon as possible because the damage to muscles and nerves will result in irreversible necrosis and contractures causing severe loss of function.
- 4▶ Fractures of the scapula often result from significant trauma and can be associated with injuries to the head, lungs, ribs, and spine.
- 5▶ The shoulder is one of the most commonly dislocated joints and most dislocations are anterior. Posterior dislocations are associated with seizures or electric shock.
- 6▶ Humeral shaft fractures occur from direct trauma to the arm or from a fall on an outstretched arm, especially in elderly patients. The radial nerve spirals around the humeral shaft and is at risk for injury, therefore a careful neurovascular exam is important.
- 7▶ Hemorrhage from pelvic trauma can be life threatening. An important first line treatment in the emergency room is the application of a pelvic binder or sheet that is wrapped tightly around the pelvis to control bleeding.
- 8▶ In spinal injury spinal stability must be assessed, and the patient immobilized until his spine is cleared. CT scan is more reliable in assessing spine injury than plain radiographs.
- 9▶ Spinal cord injuries should be triaged to trauma centers since trauma center care is associated with reduced paralysis.
- 10▶ According to the CDC and the National Health Interview Survey approximately 50 million adults (22% of the US population) have been diagnosed with some form of arthritis. This number is projected to grow to an astounding 67 million adults by 2030 (or 25% of the U.S. population).
- 11▶ Weight loss of as little as 11 pounds has been shown to decrease the risk of developing knee osteoarthritis in women by 50%. Similarly, patients who engage in regular physical activity have been found to have lower incidence of arthritis.
- 12▶ Smaller incisions come with the disadvantage of decreased visualization intra-operatively and associated risks of component malposition, intraoperative fracture and nerve or vascular injury. The only documented benefit of minimally invasive techniques appears to be improved cosmesis.

INTRODUCTION

Orthopedic surgery is a specialty with which every physician should be familiar. Anyone who cares for patients in an outpatient or emergency room setting will find that the majority of presenting complaints involve the musculoskeletal system. A basic understanding of musculoskeletal anatomy is assumed, and understanding the principles of care for musculoskeletal trauma is essential.

For physicians, the field of orthopedics offers an array of subspecialties with such diversity that it seems that “there is something for everyone.” Trauma specialists have the satisfaction of physically putting complex fractures back together. Sports medicine offers remarkably rapid recovery in athletes who have suffered fibrocartilage tears with ever improving arthroscopic techniques and instrumentation. Spine surgeons see remarkable results from their minimally invasive microscopic techniques, while also managing massive deformities with new instrumentation and open surgery. Joint reconstruction is one of our most exciting subspecialties, working with orthopedic bioengineers to develop improved designs, biomaterials, and minimally invasive surgical approaches to return function faster for patients crippled by arthritis and injury. Musculoskeletal oncology offers the intellectual challenge of arriving at appropriate differential diagnoses as well as the technical challenge of limb salvage and major reconstructive surgery. Pediatric orthopedics is an especially challenging and rewarding

subspecialty because of the remarkable ability of children to heal even severe injuries rapidly and completely. The incredible array of congenital and developmental disorders makes pediatrics a uniquely intellectually challenging field as well. The authors hope that our readers will share our enthusiasm for orthopedic surgery and all of its subspecialties: trauma, sports, spine, joint replacement, musculoskeletal oncology, and pediatric orthopedics.

ORTHOPEDIC TRAUMA

Introduction

Musculoskeletal injuries resulting from trauma include fractures of bones, damage to joints, and injuries to soft tissues. Long bone fractures can be described as transverse, oblique, spiral, segmental, or comminuted (Fig. 43-1). The goals of treating musculoskeletal injuries are to restore the normal anatomy, immobilize injured extremities for both pain relief and to allow for healing, and to repair or reconstruct these injuries to restore function.

Fractures frequently result from high energy trauma as well as from falls onto an extremity (Fig. 43-2). The majority of fractures can heal well with immobilization, which stabilizes the fracture while new bone forms at the fracture site. Methods of immobilization can vary and depend on the fracture being treated. The most common tool used in orthopedics to

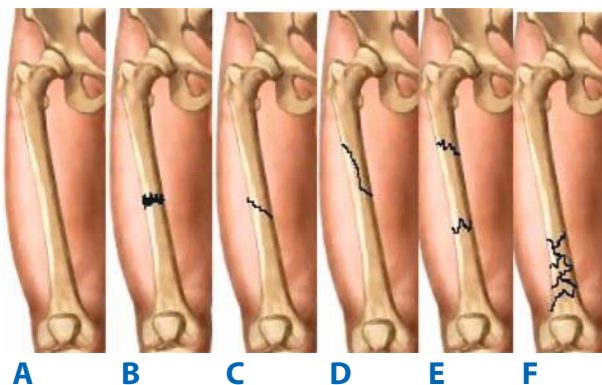


Figure 43-1. Types of fractures **A.** normal femur, **B.** transverse, **C.** oblique, **D.** spiral, **E.** segmental, **F.** comminuted.

treat fractures is immobilization with a splint or cast, and their proper application is important to successfully treat the injury without causing additional problems. A successful splint contains adequate padding on the underlying skin, and particularly over bony prominences, to prevent pressure or burns that can be caused by plaster. Splints, which are not circumferential, are preferred for acute injuries because they allow room for swelling which inevitably occurs after a fracture.

Fractures that are displaced or angulated require closed reduction to properly realign the bone. This is done using analgesia, local or general anesthesia, and often muscle relaxation. Reduction is performed with axial traction and reversal of the mechanism of injury in order to restore length, rotation, and angulation. A splint is then applied and can be gently molded to help hold the reduction in place. It is important to obtain X-rays after a close reduction to verify acceptable alignment of the fracture, and to perform a neurovascular exam to ensure the splint is not too tight.

For certain fractures, splint or cast immobilization alone is not enough and in these instances internal fixation is used.



Figure 43-2. Transverse tibia fracture and segmental fibula fracture.

The main principle of orthopedic implants for fracture care is to create a stable construct that will allow the fracture to heal in proper alignment. Screws can be placed across a fracture to create compression at the fracture site, which promotes healing. Plates can be placed on the cortex of bones and held with screws, which creates a long area of fixation to stabilize the fracture. Intramedullary rods are commonly used for long bone fractures, such as the femur and tibia (Fig. 43-3A). Prior to their placement, the marrow in the canal is usually removed with a reamer. The rod is then inserted into the canal. Screws can then be placed across the cortices of the bone through holes in the rod proximal and distal to the fracture to create a locked construct that further stabilizes the rod (Fig. 43-3B). In situations where patients are severely injured and cannot safely undergo surgery, or when the soft tissues are too swollen or injured to allow for surgical incisions to be safely made, an external fixation device can be used to temporarily immobilize the fracture. External fixators involve pins placed in bone proximal and distal to the fracture through healthy tissues that are connected by strong rods on the outside extremity, creating a stable construct.

Open Fractures

An open fracture occurs when the bone breaks through the skin. These typically result from high energy injuries and are often associated with significant damage to the surrounding soft tissues and contamination of the wound (Fig. 43-4A). These injuries require immediate irrigation and debridement in the operating room and treatment with antibiotics to prevent wound infections and osteomyelitis (Fig. 43-4B). They can also cause injuries to surrounding vessels and nerves, which must be addressed as well. Often, definitive treatment of the fracture is delayed until the wound is sufficiently cleaned and healthy soft tissue is available to cover the fracture.

Compartment Syndrome

Compartment syndrome is an orthopedic emergency caused by significant swelling within a compartment of an injured extremity that jeopardizes blood flow to the limb. Increased pressure within the compartment compromises perfusion to muscles and can cause ischemia or necrosis. Patients complain of pain and numbness, and passive stretch of muscles within the compartment causes severe pain. While the diagnosis is based on clinical exam, pressures can be measured with needles placed into the compartment, which is necessary in unconscious patients who will not show these exam findings. When compartment syndrome is suspected, emergent fasciotomy must be performed in which the overlying tight fascia is released through long incisions. These must be done as soon as possible because the damage to muscles and nerves will result in irreversible necrosis and contractures causing severe loss of function.

TREATMENT OF FRACTURES AND DISLOCATIONS

Clavicle Fractures

Fractures of the clavicle are one of the most common fractures in orthopedics. They typically occur following a fall onto the shoulder and the majority of clavicle fractures occur in the middle third of the clavicle. Since the bone is subcutaneous, the fracture is often evident on inspection. Most clavicle fractures can be treated nonoperatively with a sling, range of motion

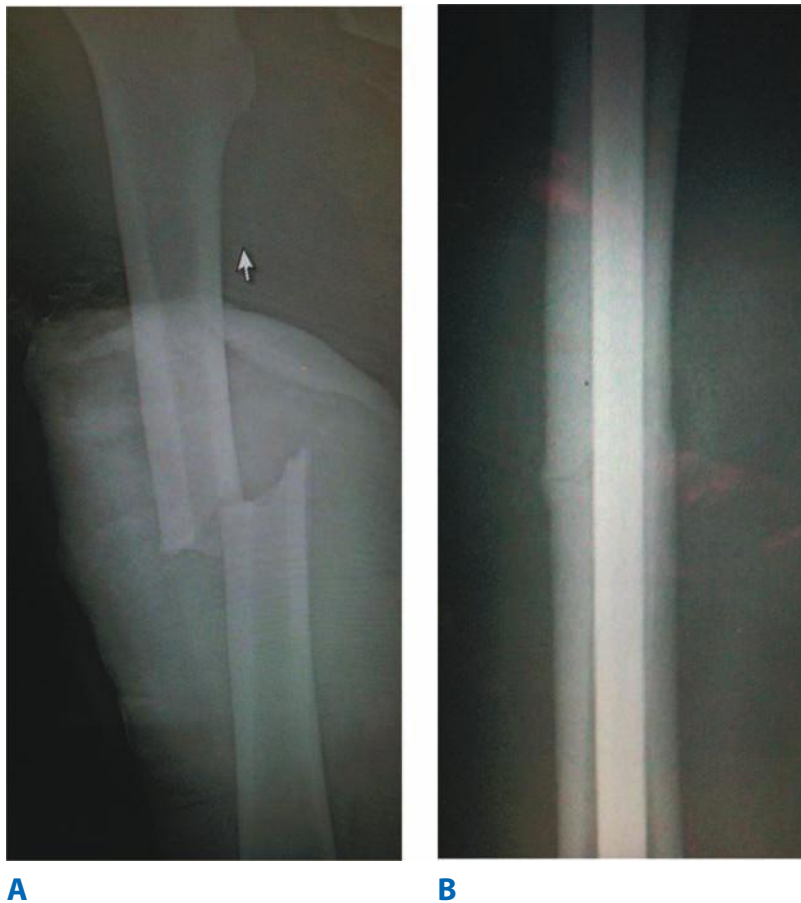


Figure 43-3. A. Transverse femur fracture. B. Intramedullary rod stabilizes femur fracture.

exercises, and gradual return to normal activities. Fractures that are significantly displaced and shortened, or that penetrate the skin, are treated with open reduction internal fixation, typically with plate and screw fixation.

Distal clavicle fractures are less common and may occur along with coracoclavicular ligament ruptures. These injuries can be more troublesome and are at risk for nonunion if the bone

ends are not in contact. If there is displacement of the fracture, surgical management is often recommended.

Acromioclavicular (AC) joint injuries occur from either a fall directly onto the shoulder or onto an outstretched hand and can result in tears of the acromioclavicular and coracoclavicular ligaments. A step-off, or separation, of the AC joint may be apparent on radiographs. The majority of



Figure 43-4. A. Open grade 3 comminuted tibia-fibula fracture (motorcycle injury). B. External fixator temporarily stabilizes grade 3 open tibia fracture.

these injuries can be treated with a sling and gentle range of motion. Injuries resulting in severe displacement of the clavicle may require open reduction and surgical repair.

The sternoclavicular (SC) joint is the only articulation between the upper extremity and the axial skeleton, and injuries to this joint are rare. Anterior dislocations occur more frequently and closed reduction can be attempted, followed by sling immobilization. Posterior SC joint dislocations can be dangerous, resulting in pulmonary or neurovascular compromise, and closed reduction under general anesthesia is recommended with a vascular surgeon present in case of vascular injury.

Scapula Fractures

Fractures of the scapula often result from significant trauma and can be associated with injuries to the head, lungs, ribs, and spine.

4► Most scapula fractures are treated nonoperatively with the exception of fractures to the glenoid. As with most intra-articular fractures, displacement of the articular surface of the glenoid is an indication for open reduction and internal fixation.

Shoulder Dislocations

The shoulder is one of the most commonly dislocated joints and most dislocations are anterior. They are often associated with injuries to the labrum (Bankart lesion), impression fractures of the humeral head (Hill-Sachs lesion), and rotator cuff tears. Posterior dislocations are associated with seizures or electric shock. Adequate radiographs are required to diagnose a shoulder dislocation, with the axillary view being the most critical. If proper X-rays are not performed then dislocations can be missed and can result in significant debilitation of the shoulder. Dislocation of the shoulders can be managed with closed reduction followed by a short period of sling immobilization.

Proximal Humerus Fractures

Proximal humerus fractures occur most frequently in elderly patients following a fall onto the shoulder, though they can also occur following high-energy trauma. They have historically been classified by the number of fracture fragments using the Neer classification, which divides the proximal humerus into 4 parts: the humeral head, greater and lesser tuberosities, and the humeral shaft. Treatment is determined by the displacement of the fracture fragments, the amount of angulation of the fracture, and the amount of comminution (which means multiple fracture fragments). If there is suspicion of an intra-articular fracture, a computerized tomography (CT) scan is often indicated. The majority of proximal humerus fractures is minimally displaced and can be treated with sling immobilization, followed by early shoulder motion and pendulum exercises. Displaced fractures and fractures involving the humeral head are at increased risk for osteonecrosis and therefore surgery is often recommended. If there is adequate bone stock and the fracture can be successfully reduced, open reduction internal fixation with plate and screw fixation is the treatment of choice. Older patients with osteoporotic bone and comminuted fractures are typically treated with a prosthetic replacement of the humeral head, or a hemiarthroplasty.

Humeral Shaft Fractures

Humeral shaft fractures occur from direct trauma to the arm or from a fall on an outstretched arm, especially in elderly patients. The radial nerve spirals around the humeral shaft and is at risk for injury, therefore a careful neurovascular exam is important. Most radial nerve injuries are neuropraxias,

or stretching of the nerve, and function typically returns in 3 to 4 months. The majority of humeral shaft fractures can heal with nonsurgical management if they are within an acceptable degree of angulation. They are treated with a coaptation splint or functional bracing, which consists of a plastic clamshell brace with Velcro straps. Close follow-up with serial radiographs is important to verify healing of the fracture, and gentle motion exercises are begun within 1 to 2 weeks. Fractures with significant angulation are most commonly treated with open reduction and plate fixation, with care to protect the radial nerve as it often lies close to the fracture site. Intramedullary nailing can also be performed, though it carries the risk of shoulder pain from the nail insertion.

Distal Humerus Fractures

Fractures of the distal humerus result from falls onto the elbow or onto an outstretched arm. Supracondylar fractures are most common, occurring above the elbow joint and do not involve the articular surface. Those minimally displaced can be treated with a posterior long arm splint, with the elbow typically flexed to 90 degrees. Fractures involving the articular surface are treated with plate fixation, and depending on the fracture pattern may require 2 plates, one placed medially and one posterolaterally. As with other intra-articular fractures, the goals of treatment are anatomic reduction of the joint surface with stable fixation, restoration of the anatomic alignment of the joint, and early range of motion. Severely comminuted fractures, especially in the elderly, may be treated with a total elbow replacement, which involves replacing the joint surfaces of the distal humerus, proximal ulna, and radial head with prosthetic components. Fractures about the elbow are notorious for developing stiffness and therefore early motion of the elbow is paramount to a successful outcome. Range of motion should be started as soon as the patient can tolerate therapy.

Elbow Dislocations

Dislocations of the elbow are common and typically occur posteriorly after a fall on an outstretched hand. A dislocation results in injury to the joint capsule and rupture of the lateral collateral ligament, though the medial collateral ligament can also be involved. They may even be associated with a fracture of the radial head, coronoid, or the epicondyles of the humerus. Simple elbow dislocations should be urgently reduced with the patient under sedation and treated briefly in a posterior long arm splint. Stiffness of the elbow is a common complication following elbow dislocations and therefore short-term immobilization (about 7–10 days) and early range of motion is recommended.

Dislocations associated with fractures may be treated surgically if there is any instability of the elbow joint. A severe injury, known as the “*Terrible Triad*,” includes an elbow dislocation, a radial head fracture, and a coronoid fracture. These are unstable injuries and require repair of the torn lateral collateral ligament (LCL), fixation or replacement of the radial head, and possible fixation of the coronoid depending on the size of the fracture fragment.

Radial Head Fractures

Most fractures of the radial head can be treated nonoperatively, simply with a sling for 1 to 2 days followed by motion exercises. However, if there is a displaced fracture or if the fracture blocks pronation or supination of the forearm, then surgery is recommended. If the fracture can be well reduced, it is fixed with 1 or 2 screws. If the radial head is fractured into multiple pieces, the treatment of choice is a radial head replacement with a

metallic implant. Excision of the radial head can also be performed, but this is reserved for elderly patients with limited demands and may contribute to elbow instability or wrist symptoms over time.

Olecranon Fractures

Olecranon fractures occur following a fall directly onto a flexed elbow. Nondisplaced fractures are treated with a splint in 45 to 90 degrees of flexion for a short time followed by range of motion exercises to prevent stiffness. Because the triceps inserts on the olecranon, the pull of the muscle often displaces the fracture, causing a loss of the ability to actively extend the elbow, and therefore should be fixed surgically. Simple transverse fractures can be fixed with a tension band construct, which consists of cerclage wiring passed through the ulna and wrapped in a figure-of-8 fashion around 2 pins placed proximally into the olecranon, creating a compressive force across the fracture to promote healing. Comminuted fractures are treated with plate and screw fixation. Because of the subcutaneous location of the olecranon, this hardware can be irritating to the patient and may need to be removed after the fracture has healed.

Forearm Fractures

Forearm fractures are common injuries that result from high energy trauma or from falls onto an outstretched arm. Both bone forearm fractures often require surgery with plate and screw fixation. The radius has a bow and rotates around the straight ulna for proper pronation and supination of the forearm, and therefore this anatomic relationship needs to be restored to maintain function. An isolated fracture of the ulna shaft, or a “nightstick fracture,” occurs from a direct blow to the side of the forearm. These can usually be treated in a cast, though fractures that are angulated or displaced can be treated with open reduction and plate fixation. A Monteggia fracture is an ulna shaft fracture along with a radial head dislocation. The radial head dislocation may be missed without radiographs of the elbow and therefore a fracture of the ulna should raise suspicion of this injury. These injuries require surgery to fix the ulna fracture with plate and screw fixation and to reduce radial head. A Galeazzi fracture is a radial shaft fracture with disruption of the distal radioulnar joint (DRUJ) at the wrist. After the radius is fixed with plate and screw fixation, the DRUJ is assessed for stability and may need wires placed across the joint temporarily.

Pelvic Fractures

Pelvic fractures are indicative of high energy trauma and are associated with head, chest, abdominal, and urogenital injuries. Hemorrhage from pelvic trauma can be life threatening and patients can present with hemodynamic instability, requiring significant fluid resuscitation and blood transfusions. The bleeding that occurs is often due to injury to the venous plexus in the posterior pelvis, though it can also be due to a large vessel injury such as a gluteal artery. Immediate resuscitation is critical and these patients may require surgical exploration or interventional radiology embolization to stop the bleeding. An important first-line treatment in the emergency room is the application of a pelvic binder or sheet that is wrapped tightly around the pelvis to help control bleeding. An external fixator may also be placed in the operating room. Other associated injuries are bladder and urethral injuries that manifest with bleeding from the urethral meatus or blood in the catheter and need to be assessed with a retrograde urethrogram.

The pelvis is a ring structure made up of the sacrum and the two innominate bones that are held together by

strong ligaments. Because it is a ring, displacement can only occur if the ring is disrupted in two places. This may occur either from fractures of the bones or tears of the ligaments. There are three main fracture patterns that occur from trauma to the pelvis. An anteroposterior force to the pelvis causes an “open book” injury pattern in which the pelvis springs open, hinged on the intact posterior ligaments with widening of the pubic symphysis. A lateral compression pattern results from a crush injury that causes fractures to the ileum, sacrum, and pubic rami. Vertical shear injuries are very unstable since they result from disruption of the strong posterior pelvic ligaments and are associated with significant blood loss and visceral injuries. Fractures of the sacrum may be difficult to see on x-ray and therefore CT scans are often needed to visualize the fracture pattern. The sacral nerves pass through foramen in the sacrum and therefore fractures that are close to this foramen can result in nerve injuries.

Treatment of pelvic fractures depends on the fracture pattern. Stable, minimally displaced fractures can be treated nonoperatively with protected weight bearing. Open book injuries in which the pubic symphysis is widened and the posterior pelvic ligaments are also injured need to be fixed surgically, which is typically performed with screws placed percutaneously through the ileum into sacrum to stabilize the pelvis posteriorly and a plate and screws over the pubic symphysis to stabilize it anteriorly. Displaced sacral fractures and iliac wing fractures are treated with screws or plates, while pubic rami fractures can usually be managed nonoperatively. While most pelvic fractures are caused by high energy trauma, elderly patients with osteoporotic bone can also suffer pelvic fractures after a fall, usually fracturing the pubic rami. Since these are stable injuries, they can be managed nonoperatively with protected weight bearing.

Acetabular Fractures

The acetabulum forms the socket of the hip joint, and fractures occur when the femoral head is driven into it in the setting of high energy trauma. CT scans are important to visualize the fracture pattern. These fractures often require surgery in order to restore a congruent, stable acetabulum, because incongruity of the hip can lead to early degenerative changes and osteoarthritis. These are best treated in the hands of experienced orthopedic trauma surgeons.

Hip Dislocations

Hip dislocations almost always result from high energy trauma and most commonly occur posteriorly. They can cause injury to the sciatic nerve, which runs directly posterior to the hip joint, and may be associated with a fracture of the acetabulum or femoral head. Hip dislocations need to be emergently reduced because of the risk of osteonecrosis of the femoral head when reduction is delayed. They can usually be reduced in the emergency room with adequate sedation and muscle relaxation, but sometimes patients need general anesthesia to aid in the reduction. If this is unsuccessful, or if a fracture fragment gets trapped inside the joint, then an open reduction is performed. Hip dislocations that are associated with a femoral head fracture are at increased risk for osteonecrosis of the femoral head and post-traumatic osteoarthritis.

Hip Fractures

Hip fractures are an extremely common injury seen in orthopedics and are associated with significant morbidity and mortality. They most often occur in elderly patients after ground level falls, are much more common in women than men, and

occur more commonly in patients with osteoporosis. Patients who suffer hip fractures are at increased risk for many complications, including deep vein thrombosis, pulmonary embolism, pneumonia, deconditioning, pressure sores, and even death, as the mortality rate in the first year following a hip fracture is around 25%. One of the most important reasons for performing surgery is to prevent these complications, and getting patients out of bed and walking as soon as possible diminishes their risk. Therefore, surgery is almost always the treatment of choice for hip fractures, and the type of surgery performed is determined by the anatomic location of the fracture and the fracture pattern. Surgery should be performed as soon as possible, typically within 24 to 48 hours; however, since many of these patients suffer other comorbidities, they must be properly medically optimized before surgery. The goals of surgery are to minimize pain, restore hip function, and allow early mobilization, the importance of which cannot be overemphasized. The functional outcome for patients following a hip fracture is largely based on their level of mobility and independence before their injury. Many patients become less independent, may require assistive devices to help them walk, and some may require a long-term nursing or rehabilitation facility.

Femoral Neck Fractures Femoral neck fractures occur with the capsule of the hip joint. The blood supply to the femoral neck and head comes from branches of the medial and lateral femoral circumflex arteries, which run along the femoral neck, and therefore fractures in this area put the vascular supply at risk and can lead to osteonecrosis. Femoral neck fractures that are nondisplaced have a low risk of disruption of blood flow and therefore can be treated with in situ internal fixation.

Three cancellous screws are placed through a small incision over the lateral proximal femur, directed up through the femoral neck and into the femoral head. Patients can usually begin protected weight bearing immediately after surgery. Displaced femoral neck fractures will likely disrupt the blood supply and therefore need to be treated with a prosthetic replacement. Most commonly a hemiarthroplasty is performed in which the femoral neck and head are replaced with a metal stem into the femoral canal and a metal head (Fig. 43-5A). Patients who have severe osteoarthritis of the hip joint and had significant arthritic hip pain before their fracture may receive a total hip replacement, in which the acetabulum is also replaced with a prosthesis, typically a plastic cup inside a metal shell (Fig. 43-5B). Patients can begin weight bearing immediately after surgery.

Intertrochanteric Hip Fractures. Intertrochanteric hip fractures occur between the greater and lesser trochanters of the proximal femur. Because the blood supply to this area is abundant, osteonecrosis is uncommon and therefore these fractures can be fixed with internal fixation. Displaced fractures need to be realigned, and this involves placing the patient on a fracture table where traction and rotation can be applied to the affected leg to reduce the fracture. There are two devices that can be used. A sliding hip screw includes a large screw placed from the lateral cortex of the proximal femur across the fracture and into the femoral neck and head, followed by a side plate along with lateral cortex of the femur, which is then fixed to the shaft with screws. A cephalomedullary nail includes a nail placed down the medullary canal from the piriformis fossa and a large screw that engages the nail as it is passed from the lateral cortex up into the neck and head. Both devices form stable constructs (though the

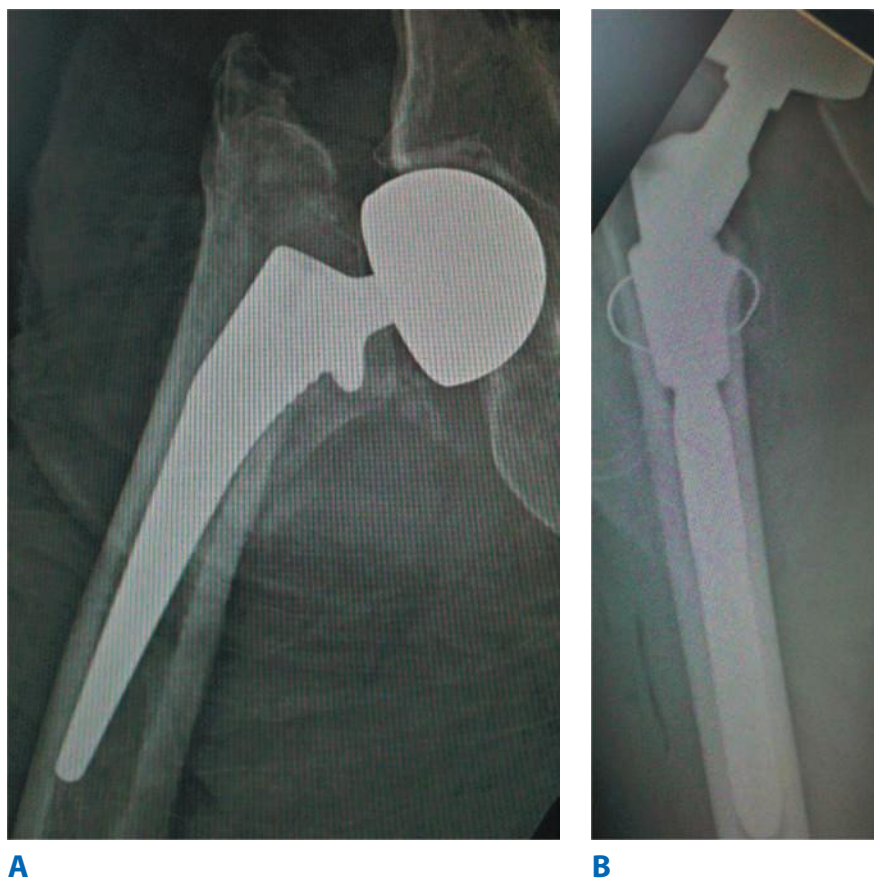


Figure 43-5. A. Failed hip hemiarthroplasty (periprosthetic fracture). B. Periprosthetic fracture repaired with modular femoral component.

cephalomedullary nail is preferred for certain fracture patterns) and allow protected weight bearing postoperatively.

Subtrochanteric Hip Fractures. Subtrochanteric hip fractures occur in the proximal femoral shaft just distal to the lesser trochanter in an area of high biomechanical stresses. While they can occur in elderly patients after a fall, they are also seen in high energy trauma. Because of the forces of muscles attached to the fractured segments, they tend to be significantly displaced and it can be difficult to reduce these fractures. They are most often treated with a long cephalomedullary nail that includes a screw distally to lock the nail in place and prevent rotation of the femur. Fractures that cannot be reduced closed on a fracture table or that are severely comminuted require open reduction followed by a cephalomedullary nail or by a plate and screws that is placed over the lateral cortex of the femoral shaft. In most cases, protected weight bearing can begin soon after surgery.

Femoral Shaft Fractures

Fractures of the femoral shaft are caused by high energy trauma and may be associated with other severe injuries. Long bone fractures, such as femoral shaft fractures, put these patients are risk for complications such as thromboembolic events and acute respiratory distress syndrome (ARDS), and therefore it is important to fix these quickly, typically within 24 hours. They are most commonly fixed with an intramedullary nail that can be placed antegrade (from the piriformis fossa or greater trochanter down the canal) or retrograde (through an incision into the knee joint and up the canal), with screws placed through proximal and distal holes to lock the nail in place, creating a stable fixation to allow weight bearing. Trauma patients who are hemodynamically unstable or who have other life-threatening injuries are treated temporarily with an external fixator until they can safely undergo surgery.

Distal Femur Fractures

Distal femur fractures are the result of a fall from a height or from high-energy trauma. They can also occur in elderly patients with osteoporotic bone after a fall onto the knee. While nondisplaced fractures in the elderly may be treated nonoperatively with a hinged knee brace and motion exercises, most require surgery. These fractures can involve the articular surface of the knee joint, so anatomic reduction of the joint surface is crucial. They are fixed with plates and screws placed over the medial or lateral cortex, depending on the fracture pattern, and early knee range of motion is encouraged to prevent stiffness. These intra-articular fractures require the patient to be nonweight bearing until the fracture shows signs of healing.

Knee Dislocations

Dislocation of the knee is a rare but devastating injury that can be limb-threatening. When the knee dislocates, the anterior cruciate ligament (ACL) and posterior cruciate ligament (PCL) are torn, and various degrees of injury occur to the LCL, medial collateral ligament (MCL), posterolateral corner, joint capsule, and menisci. The danger however is due to the close proximity of the popliteal artery that runs directly behind the knee, which may kink or suffer a tear of the intimal wall when the knee dislocates. A neurovascular exam is extremely important, followed by immediate reduction of the knee and repeat exam of the pulses. If there is evidence of diminished or absent pulses, an angiogram must be performed, and vascular surgery may need to perform emergent vascular repair. With regard to the

ligamentous injuries, an MRI will identify what structures have been torn. Because a dislocation causes so much damage to the knee, multiligamentous reconstruction is recommended in order to stabilize the knee joint. Stiffness and instability of the knee are common complications after this injury.

Patella/Extensor Mechanism Injuries

The extensor mechanism is comprised of the quadriceps tendon, the patella, and the patella ligament and functions to extend the knee. Injuries can result after a fall directly onto the knee or from forcible contraction of the quadriceps. It is important to examine the knee for the ability to actively extend the knee, since quadriceps tendon ruptures, patella fractures, or patella ligament ruptures can result in a loss of active knee extension, requiring surgery. Nondisplaced patella fractures can be treated nonoperatively with a cast or knee immobilizer, holding the knee in full extension, and weight bearing is permitted. Displaced or comminuted fractures require surgery with either tension band wiring or screws. Acute osteochondral fractures can be managed with internal fixation (Fig. 43-6A and B). Quadriceps tendon and patella ligament ruptures with loss of active knee extension are treated with suture repair. After surgery, the knee is held in extension and knee flexion is slowly increased over several weeks using a hinged knee brace.

Patella dislocations are common injuries that occur when the femur is forcibly internally rotated on an externally rotated tibia while the foot is planted on the ground. They typically dislocate laterally and often relocate spontaneously. Patients present with a significant knee effusion and on physical exam may elicit a positive apprehension test, in which a lateral force to the patella elicits pain and the sensation of an impending dislocation. Dislocated patellas can be reduced by extending the knee and manual reduction, and are treated with temporary knee immobilization. There is a high risk for recurrent dislocations, which may require surgical intervention. Osteochondral injuries to the trochlear groove and patella may be managed with the Draenert technique of autologous osteochondral transplant (Fig. 43-7A and B).

Tibial Plateau Fractures

The tibial plateau is comprised of the articular surfaces and underlying cancellous bone of the medial and lateral plateaus of the proximal tibia. Fractures of the plateau result from axial loads sustained in falls from a height or high energy trauma, and are often associated with injuries to the menisci and cartilage of the knee. Fractures can involve the medial, lateral, or both plateaus with significant comminution, angulation, and depression, creating a challenging injury to fix. A CT scan is important to visualize the intra-articular involvement of the fracture. Minimally displaced fractures may be treated nonoperatively with strict nonweight bearing until the fracture heals. Fractures associated with displaced articular fragments require surgery in order to restore the smooth contour of the articular surface. They are treated with plates and screws placed medially, laterally, or both. Since there is often a depression of the cancellous bone, bone graft or bone substitutes may be needed to buttress the articular surface and restore the anatomic alignment of the tibia. Patients are kept strictly nonweight bearing for several weeks until the fracture begins to heal, though early range of motion is encouraged. Repair of ligament or meniscus injuries may also be indicated at the time of surgery. Knee stiffness and osteoarthritis are common complications of these injuries.

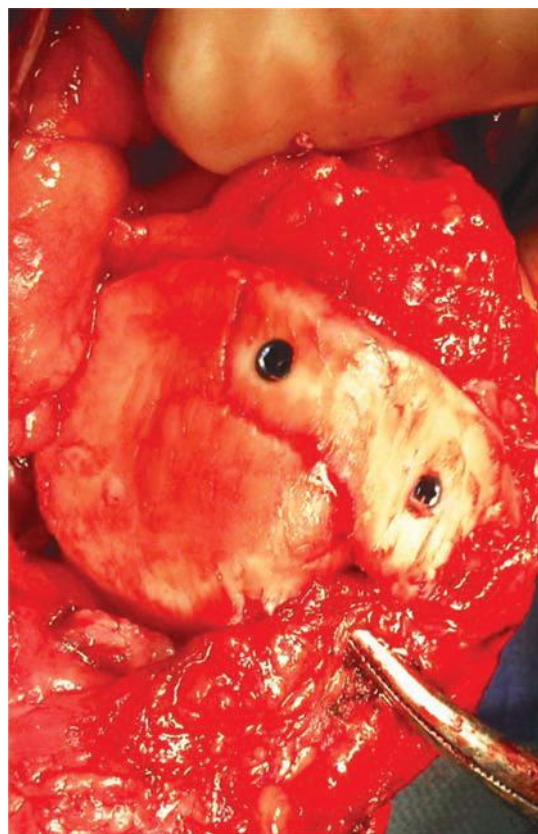
**A****B**

Figure 43-6. **A.** Osteochondral Patella Fracture. **B.** Internal fixation of osteochondralpatellar fracture.

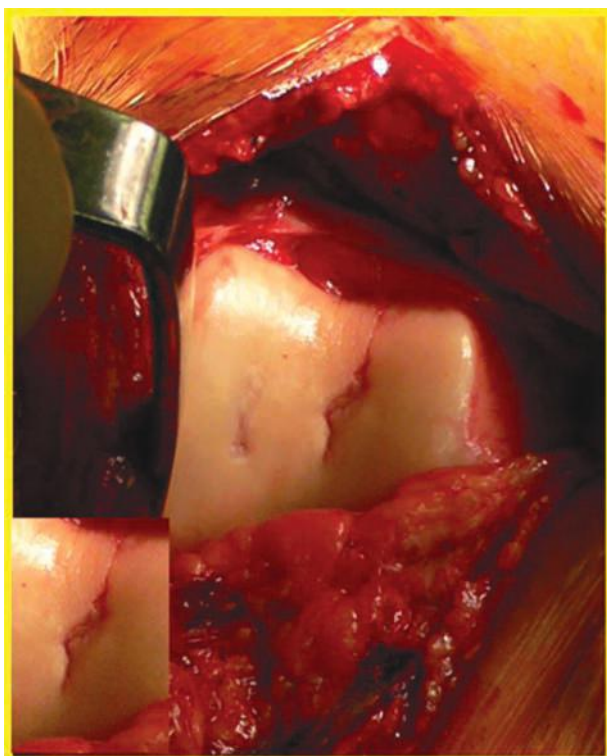
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Figure 43-7. **A.** Knee traumatic articular lesion (trochlear groove). **B.** Lesion repaired with Draenert technique (autologous osteochondral transplant).

Tibial Shaft Fractures

Tibial shaft fractures are the most common long bone fractures and they occur following high energy trauma, direct blows, and severe twisting injuries. Trauma and direct blows to the tibia result in transverse or comminuted fracture patterns, while torsional injuries cause spiral fractures. Fractures with minimal angulation can be treated with reduction and casting, followed by transition to a functional brace and slow return to weight bearing, and may need to be immobilized for several months since these fractures can be slow to heal. Most tibial shaft fractures, especially comminuted and angulated fractures, are treated with an intramedullary nail placed down the tibial canal, with interlocking screws placed proximally and distally, and weight bearing can begin soon after surgery. Plate and screw fixation can also be used, however since the tibia is subcutaneous, hardware placed along the shaft can increase the risk of wound breakdown, and therefore intramedullary nailing is the preferred treatment. Fibula shaft fractures often occur along with tibial shaft fractures, though they usually heal well without surgery.

Tibial Plafond (Pilon) Fractures

The tibial plafond is the distal tibial articular surface of the ankle joint. Pilon fractures are typically high energy injuries from axial compression or a shear force. These injuries can cause significant soft tissue injury, severely comminuted intra-articular fragments, and wound healing problems, making these fractures very difficult to treat. Due to the soft tissue injury, these fractures are initially treated with external fixation until the swelling subsides, which may take several days to weeks. The goals of surgery are to restore the articular surface, fix the fibula in order to maintain and establish anatomic length, bone graft any cancellous bone defects, and stabilize the distal tibia with plate and screw fixation. Patients are kept nonweight bearing for many weeks until the fracture heals. Despite best efforts, patients may suffer from ankle pain and stiffness, arthritis, wound healing problems, infection, nonunion, and some patients eventually need ankle fusion in the future.

Ankle Dislocations

The ankle joint is a complex hinge joint comprised of the distal tibial plafond, medial malleolus, and lateral malleolus and their articulation with the talus. Several ligaments also contribute to the stability of the ankle joint, including the deltoid ligament medially, the syndesmotic ligaments between the tibia and fibula, and the anterior talofibular, posterior talofibular, and calcaneofibular ligaments laterally. Dislocations of the ankle joint result from a severe twisting injury and often occur with fractures. At times, dislocations can place significant pressure on the overlying skin and can cause neurovascular compromise, therefore prompt reduction is extremely important followed by splinting.

Ankle Fractures

Ankle fractures are very common and result from a twisting injury to the ankle. The patterns of ankle fractures depend on the direction of force and the position of the foot and ankle at the time of injury. The goals of treating ankle fractures are to restore the anatomy of the ankle joint and to restore the length and rotation of the fibula. Initial treatment includes closed reduction and placement of a well-padded splint in order to protect the skin. Swelling can be a significant problem so elevation of the foot is encouraged. If surgery is to be performed, it is usually delayed 1 to 2 weeks until the swelling decreases to limit the risk of wound healing problems.

Lateral Malleolus Fractures Isolated fractures of the lateral malleolus require anatomic reduction of the fracture in order to restore normal ankle joint congruity. The talus can sublux laterally following lateral malleolus fractures, and even 1 millimeter of talar shift decreases the surface contact between the talus and the tibia by 40%, increasing the risk of developing arthritis. Closed reduction and casting can be successful, however if the fracture cannot be adequately reduced, then open reduction internal fixation of the fibula is done with plate and screw fixation.

Medial Malleolar Fractures An isolated fracture of the medial malleolus is usually an avulsion-type injury. Minimally displaced fractures can be treated with a cast or walking boot, while displaced fractures are fixed with screws placed up through the tip of the malleolus.

Bimalleolar Fractures Fractures to both the medial and lateral malleoli often require surgery. These injuries are more unstable and the talus will often sublux or completely dislocate laterally. They are treated by reducing and fixing both malleoli during surgery. Occasionally, the posterior articular surface of the distal tibia, or posterior malleolus, can be fractured as well, resulting in a trimalleolar ankle fracture. Often it is a small fragment and does not need to be fixed, however if it involves >25% of the articular surface it should be fixed with screws placed either anteriorly or posteriorly.

Syndesmosis injuries The syndesmosis is comprised of several ligaments between the distal tibia and fibula that provide stability to the ankle joint by resisting axial, rotational, and translational forces. The syndesmosis can be disrupted at the time of ankle fractures and requires special attention. Widening of the space between the distal tibia and fibula after fixing the fractures is indicative of a syndesmosis injury and it is treated with 1 or 2 screws placed laterally from the fibula into the tibia, parallel to the ankle joint. Patients are kept non-weight bearing for several weeks. The screws are often removed after 12 weeks, though they can be left in place and are typically asymptomatic.

Calcaneal Fractures

Calcaneal fractures occur following a fall from a height and are often associated with other injuries, including lumbar spine fractures. These injuries are often intra-articular and can result in collapse of weight-bearing posterior facet of the calcaneus. CT scans are useful to better visualize the fracture pattern. Most fractures can be treated nonoperatively in a well-padded splint and patients are kept nonweight bearing for up to 12 weeks. Displaced intraarticular fractures can be treated surgically once the swelling subsides with lag screws or with a thin plate and screw fixation. Despite adequate treatment, calcaneal fractures can be debilitating injuries, leading to significant heel pain and arthritis.

Talus Fractures

Fractures of the talus commonly result from forced dorsiflexion of the ankle, causing the talar neck to impact on the anterior distal tibia. The blood supply to the talus can be jeopardized after a fracture and may lead to osteonecrosis, which is an unfortunately common complication following talus fractures. Nondisplaced fractures are treated with a cast and have a 15% risk of osteonecrosis, while displaced fractures are often treated surgically with screw fixation. There is a high risk of osteonecrosis, ranging from 30% to 100%, and a high risk of arthritis.

Foot Fractures

The tarsal bones, including the navicular, the cuboid, and the three cuneiform bones, link the hind foot to the metatarsals and provide mechanical stability to the arch of the foot. Isolated fractures to these bones are rare and are often treated nonoperatively with a cast or boot. The Lisfranc ligament, which connects the 2nd metatarsal head to the medial cuneiform, is an important stabilizer of the midfoot. Lisfranc injuries can be seen following torsional forces to the foot or from crush injuries. These injuries often require surgery since anatomic reduction is extremely important for a successful outcome. Metatarsal fractures similarly result from twisting or crush injuries and most can be treated nonoperatively with a hard-soled shoe and weight bearing as tolerated. The base of the 5th metatarsal, however, warrants close attention. Fractures at the metaphyseal-diaphyseal junction of the proximal 5th metatarsal (Jones fractures) can jeopardize blood flow and are at risk for nonunion. Therefore, Jones fractures need close follow-up to assess for healing and may need screw fixation. Injuries to the metatarsal-phalangeal joints and phalangeal fractures can be treated symptomatically or with buddy taping with weight bearing as tolerated in a hard-soled shoe.

INTRODUCTION

Sports Medicine

Sports medicine deals with the prevention and treatment of injuries related to sports and exercise. These injuries encompass various areas in the musculoskeletal system. In recent years, sports-related injuries have increased and the sports medicine field has been expanding. The growth in sports and sports-related injuries has likely to do with: a) that athletes participate in sport-specific training year round (and in multiple sports) rather than just seasonal training, b) that there has been an increase in “weekend warriors,” c) that patients have become more aware of physical fitness, are better educated, and have higher performance expectations, and d) that more people undertake recreational activities.

The orthopedic subspecialty of sports medicine treats a broad spectrum of patients, ranging from children who have just started participating in their first sports to the specialized care of professional athletes. Medical treatment of athletes, recreational or professional, can be complex as short- and long-term outcomes are influenced by the higher demand that athletes put on their bodies. Additionally, the orthopedic sports medicine specialist does not only treat the patient’s injuries, but also has to consider the return to activity in a later stadium. “Getting back in the game” is sometimes subject to pressure from third parties (e.g., team members, coaches, parents, fans), which makes treatment and the rehabilitation a challenging process.

Surgical intervention for ligament and cartilage injuries in sports medicine patients is usually done using arthroscopic techniques. The most frequently injured joints are the shoulder, hip and knee. Therefore, treatment of common injuries in these joints will be the scope of this paragraph.

SHOULDER

Rotator Cuff

Rotator cuff injuries are among the most common reasons to visit an orthopedic sports specialist. Often, these injuries are associated with either forceful or repeated overhead or pulling movements. The rotator cuff provides shoulder movement and

glenohumeral joint stability and injuries typically lead to pain, weakness and restricted movement of the arm. Over recent years, the treatment of the rotator cuff injuries has considerably improved with regard to indication for surgery, surgical techniques and rehabilitation protocols. With the introduction of arthroscopy, shoulder surgery has become less invasive with all advantages associated. Currently, it has been established that arthroscopic techniques are equal or superior to open techniques for most indications. Controversies surrounding rotator cuff repair remain and include, but are not limited to, use of acromioplasty, enhancement of healing with orthobiologics (Fig. 43-8), single- vs. double-row fixation and the treatment of massive or large tears. Rehabilitation after surgery plays an important role to restore strength, motion and function and to enable the patient to return to sports. Typically, rehabilitation is made up of three consecutive stages: immobilization, passive exercise, and active exercise. Immobilization and passive exercise usually start in the first 4 to 6 weeks after surgery. Immobilization can be established by using a sling and passive exercise should be initiated by the therapist. The therapist moves the arm in different positions to improve range of motion (ROM) while providing support. After 4 to 6 weeks, active exercises can be gradually introduced. At 8 to 12 weeks, muscle strength and improvement of arm control are increased by starting a strengthening exercise program.

Shoulder Instability

The most common etiology for shoulder instability is related to trauma, especially shoulder dislocation. After a shoulder has dislocated, it becomes vulnerable to repeat episodes of instability and may develop to being a chronic problem. Most of the shoulder’s stability is provided by the rotator cuff and shoulder capsule. The most common dislocation is in the anterior-inferior direction, although posterior dislocations do occur. Typically, patients with an anterior dislocation present with pain and an internally rotated shoulder. Younger patients are more susceptible to suffer from repeat dislocations than older patients.⁶⁻⁸ The position of the humeral head with respect to the glenoid and other bony pathology can be identified with radiographs. Views from different angles should be obtained to thoroughly evaluate; an anterior-posterior (AP) view, along with glenoid (axillary) view, and a “Y” view of the shoulder are recommended in assessing this injury. Since most of the shoulder’s stability is provided by soft tissue, usually this is also injured. Following successful reduction magnetic resonance imaging (MRI) should be obtained to identify underlying causes and concomitant injuries.

Relocation of the shoulder is generally accomplished with the patient in supine position and the arm under gentle traction and slight abduction. Some sedation is helpful as it relaxes the patient’s musculature and relieves the pain. Whether or not to immobilize a first-time-dislocated shoulder or not, remains controversial, as well as the position of immobilization or the early surgical repair of capsulolabral structures. Prolonged immobilization is not recommended since this will often lead to substantial stiffness in the shoulder and does not appreciably decrease the redislocation rate. A small minority of patients with atraumatic multidirectional instability can generally be treated with shoulder rehabilitation. Unfortunately, many patients experience recurrent dislocations, in which case surgical stabilization of the shoulder should be considered. Many open stabilizing procedures have been described and, depending on etiology,

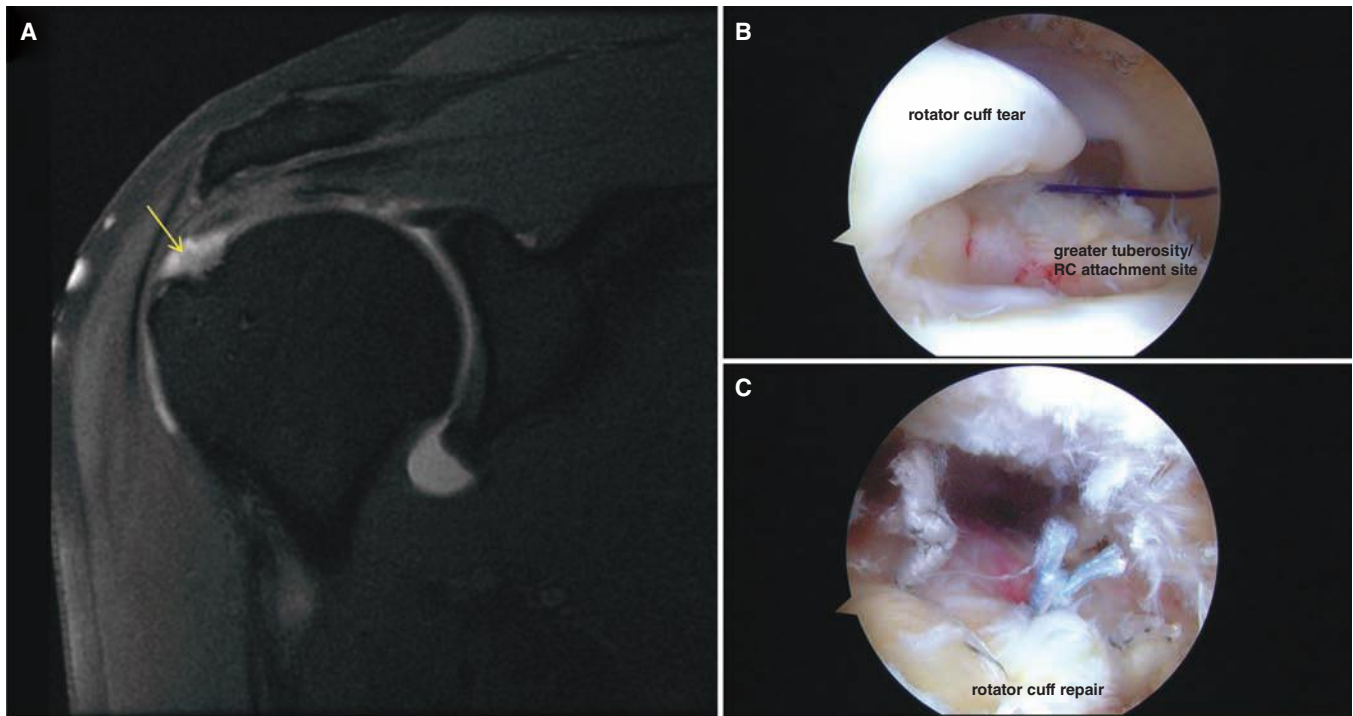


Figure 43-8. Imaging and treatment of rotator cuff tears. **A.** MRI coronal T2 image showing a full-thickness and moderately retracted tear (arrow) of the supraspinatus tendon. **B.** Arthroscopic image showing the supraspinatus tendon tear as viewed from a posterior portal during the surgery. **C.** Arthroscopic image showing completion of repair of the supraspinatus tendon tear using suture anchors imbedded in the greater tuberosity of the humerus and attached sutures that capture and reduce the torn tendon to its native insertion site.

many are still being applied such as the open Bankart repair, Latarjet procedure, remplissage and humeral head restoration. However, arthroscopic soft-tissue restoration has been the front-line treatment for recurrent instability. After surgery, the shoulder is temporarily immobilized with a sling. When the sling is removed, exercises to rehabilitate the ligaments, improve ROM and prevent from scarring, will be started. Strengthening exercises will gradually be added to the rehabilitation plan.

Superior Labrum and Biceps Tendon

The labrum helps to deepen the socket and stabilizes the glenohumeral joint. Additionally, it serves as an attachment point for many of the shoulder ligaments, as well one of the biceps tendons. A superior labrum anterior and posterior lesion may occur in the superior part of the labrum, usually anterior and posterior to the attachment of the biceps tendon, with occasional involvement of the biceps tendon in certain cases. Injuries to the superior labrum can be caused by trauma or by repetitive shoulder motion. Radiographs are generally obtained to evaluate for concomitant injuries or osteoarthritic changes. The labrum itself, and other soft tissue, is better visualized with MRI with addition of a gadolinium arthrogram adding sensitivity for labral injury detection (Fig. 43-9).

Conservative and operative treatments have had mixed results depending on the patient's age, activity level, type of tear and presence of concomitant injuries. If symptoms do not improve with adequate physical therapy and/or nonsteroidal anti-inflammatory drugs (NSAIDs), surgical intervention is usually indicated. Some SLAP injuries involve the biceps tendon, which may require either tenotomy or tenodesis.^{10,11}

After surgical labrum repair, the shoulder needs to be immobilized to protect the repair and allow for healing.

Usually a sling is used for 4 weeks after surgery. Then a physical therapy program will gradually start improving ROM and prevent from scar formation and stiffness to develop. As healing progresses, exercises to strengthen the shoulder muscles and the rotator cuff will gradually be added to the program around 4 to 6 weeks after surgery. Return to early interval throwing can generally be allowed around 3 to 4 months after surgery.

Impingement Syndromes

After minor trauma or repetitive injury, patients may experience pain and discomfort which can be due to irritation of the tissues in the subacromial space. In many cases these shoulder impingement syndromes are caused by simple bursitis or tendonitis of the long head of the biceps or supraspinatus tendon.⁵ Occasionally, impingement syndromes can progress to tears of the supraspinatus tendon, which can be confirmed by MRI or ultrasound.

The goal of treatment is to reduce pain and restore function. Initial treatment is generally nonsurgical and based on rest, NSAIDs, and physical therapy. If pain is not relieved, an injection of a local anesthetic and a cortisone preparation may be helpful.

If conservative treatment does not relieve pain, surgery is recommended, with the goal to excise the bursa and create more subacromial space. Generally, surgery is performed arthroscopically and encompasses bursectomy and subacromial decompression via acromioplasty. If the rotator cuff (supraspinatus tendon) is also injured, arthroscopic repair is usually indicated to restore function, sometimes is accompanied by a bony resection of the inferior portion of the acromion.

The Acromioclavicular Joint

The acromioclavicular joint is a gliding synovial joint and not very mobile. The joint is stabilized by three ligaments: the superior acromioclavicular ligament, the inferior acromioclavicular

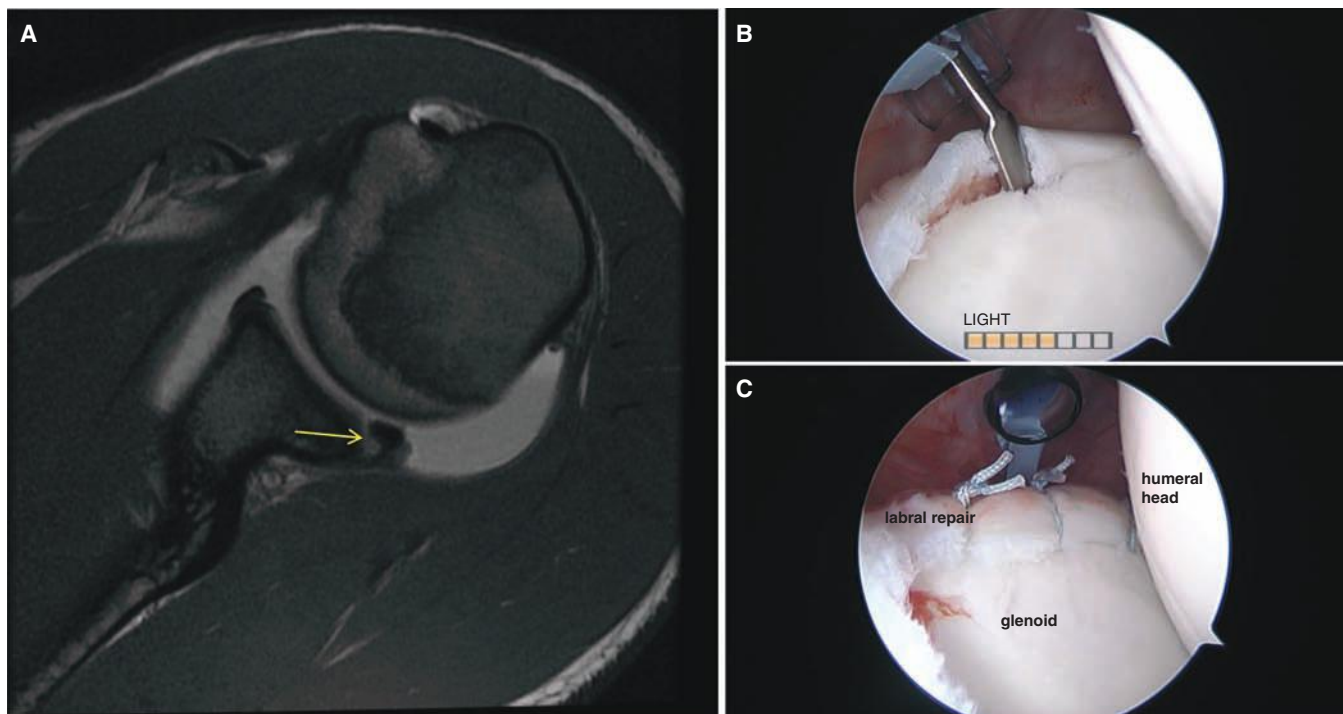


Figure 43-9. Imaging and treatment of a shoulder glenoid labrum tear. **A.** MRI axial T1 image showing a tear of the posterior superior labrum (arrow). **B.** Arthroscopic image with the patient in the lateral decubitus position showing detachment of the torn labrum away from the glenoid. **C.** Arthroscopic image demonstrating repair of the labrum to its attachment site using anchors in the glenoid and sutures that fixes the labrum to the glenoid.

ligament, and the coracoclavicular ligament. Injuries to these ligaments are commonly sustained playing contact sports such as football and ice hockey and may cause displacement of the joint. An acromioclavicular sprain is referred to as a shoulder separation and type I and II are usually treated symptomatically. Controversy exists however regarding early or delayed surgical reconstruction for type III tears. Frank tearing of the coracoclavicular ligaments, associated with significant displacement, is oftentimes reconstructed surgically.

KNEE

The knee is the largest joint in the human body and is a pivotal hinge joint, which allows flexion and extension as well as a medial and lateral rotation. The knee bears tremendous axial loads as well as torsional and shear forces, making it vulnerable to both acute injury and the development of osteoarthritis. In sports, the major stabilizing structures such as the ACL and the medial collateral ligament (MCL) are frequently injured. Other frequent knee injuries are to the menisci, posterolateral corner, the posterior cruciate ligament (PCL) or patellofemoral.

Menisci

The menisci are crescent-shaped pieces of fibrocartilage shaped that provide joint stability, shock absorption, load distribution, and proprioception. Sudden meniscal tears often happen during sports, usually during contact or while squatting and twisting the knee. Typical symptoms associated with meniscus injury are pain, stiffness and swelling, catching or locking of the knee, buckling or “giving way” and impaired ROM. Radiographs are typically obtained to assess possible concomitant injuries, the

presence of (early) osteoarthritis, and leg alignment. However, since menisci do not show on radiographs, an MRI is obtained to assess the status of the menisci and the soft tissue surrounding the knee joint (Fig. 43-10). Small tears on the outer edge of the meniscus may not cause symptoms and—provided the knee is stable—nonsurgical treatment may be sufficient.

The most commonly performed surgical procedure for meniscus tears is partial (subtotal) meniscectomy. However, it has become increasingly clear over recent years that preservation of the load-distributing function of the meniscus is important in preventing from development of early osteoarthritis. Research into the use of orthobiologics (e.g. microfracture of the notch, fibrin clot) for meniscal repairs has expanded the indications for repair over (subtotal) meniscectomy.^{15–19} Tears have been reported in virtually all portions of the meniscus, with radial and longitudinal tears being the most common. Tears of the root of the meniscus are less common, but are increasingly being recognized as devastating injuries that cause serious alterations of knee contact forces. Surgical techniques are developing to repair the root to restore its function.^{20,21} Meniscus transplantation may be an option for young patients with a largely deficient meniscus.²²

The paradigm of treatment of torn menisci is shifting thanks to the development of superior surgical techniques, use of orthobiologics and promising first results with root repair and meniscus transplantations. Physicians must be further educated on the significance of meniscal preservation when there is potential for healing.

Directly after surgery, the knee is immobilized with a brace and weight bearing is protected to allow the meniscus to heal. When healing is complete, ROM and strength will need

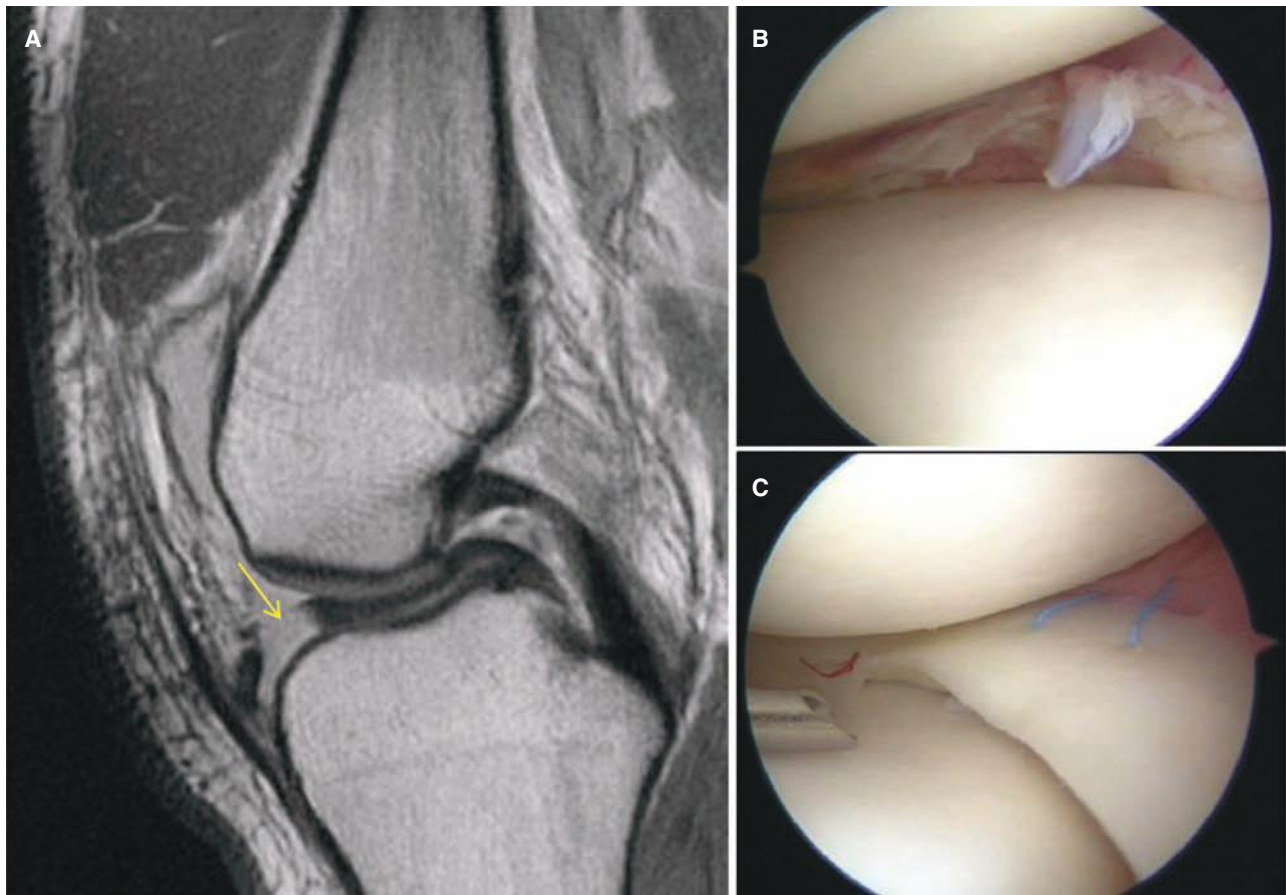


Figure 43-10. Imaging and treatment of a knee lateral and meniscus tear. **A.** MRI sagittal T2 image of the knee showing a displaced bucket-handle lateral meniscus tear (arrow). **B.** Arthroscopic image showing the remnant rim of the lateral meniscus prior to reduction and fixation of the torn bucket-handle fragment. **C.** Arthroscopic image after the torn segment is reduced and fixed to the remaining meniscus and the lateral capsule using suture.

to be regained. Physical therapy is an integral component of healing and return to play, which usually is allowed between 4 to 6 months after surgery.

Collateral Ligaments

The MCL is the most frequently injured knee ligament, which usually occurs after excessive valgus stress of the knee. Oftentimes, this is associated with (medial) meniscus injury and sometimes with an ACL. The combination of MCL, medial meniscus, and ACL injury is also known as the “unhappy triad” and occurs most commonly in contact sports.

The MCL has good healing potential and grade I and II injuries usually improve with bracing and activity modification. Grade III injuries may also improve with conservative treatment and often these injuries are treated non-operatively initially. The majority of MCL injuries occur in the mid-substance or at the femoral insertion side. There is a small subset of tibial sided grade III tears though, that is associated with worse clinical outcome and surgical repair is more often advocated. Reconstruction is rare, since surgical repair is usually effective in restoring the MCL. Lateral collateral ligament (LCL) injuries are much less common than MCL ligament injuries, but similarly most often managed conservatively.

With return of ROM and normal gait pattern, patients are functionally progressed towards return to sports. A functional brace during sports is advised.

Cruciate Ligaments

The cruciate ligaments are situated centrally within the intercondylar notch of the knee. The biomechanical function of both the ACL and the PCL is complex and three-dimensional, but to simplify: both play an important role in providing antero-posterior and rotational stability of the knee.

ACL tears are a common sports injury, especially in sudden cutting and stopping sports (e.g. soccer, basketball) or contact sports (e.g. football). A torn ACL will result in altered knee biomechanics and kinematics and thus potentially lead to the early development of degenerative changes in the knee joint. Since a torn ACL will not heal without surgery, surgical ACL reconstruction is generally treatment of choice in patients who are young and active. Patients with a more sedentary lifestyle and who experience no persisting or disabling instability in daily life, may be effectively treated with conservative management (i.e., bracing and physical therapy).

A patient with an ACL tear typically presents with pain and swelling, instability, loss of ROM, joint line tenderness (with associated meniscus injury), and discomfort while walking. Radiographs are obtained to evaluate joint condition and possible associated osseous injuries. To visualize the ACL and other soft tissue in the knee however, an MRI should be obtained. Although an MRI is not required to make the diagnosis, the information it provides is invaluable with regard to objectifying anatomic characteristics by taking measurements,

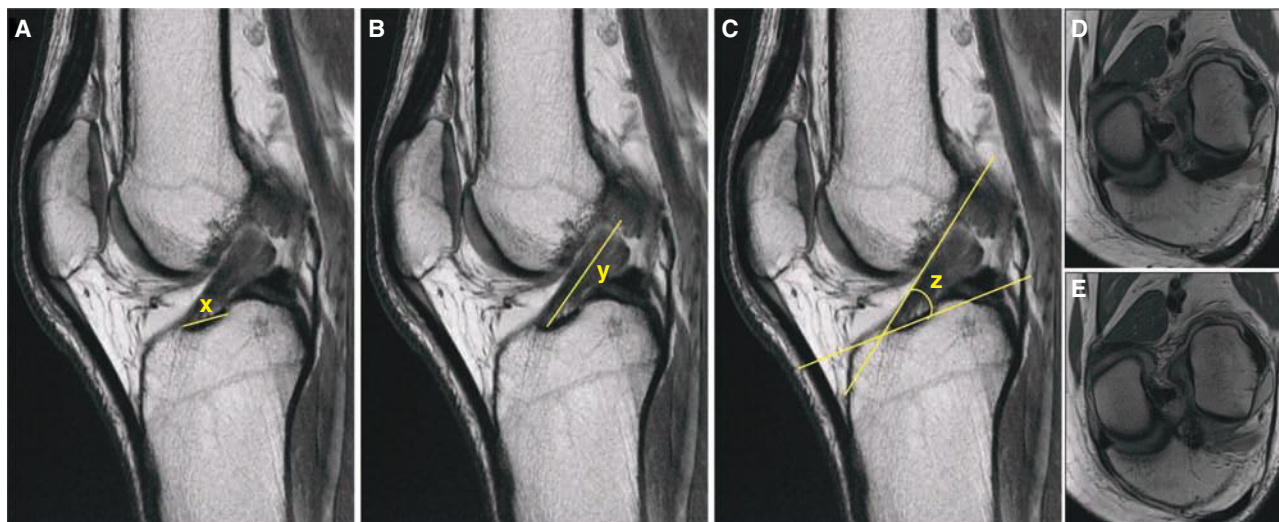


Figure 43-11. MR imaging of a torn ACL. (A-C) Proton density sagittal cuts; showing anteroposterior tibial insertion site length measurement “x”, intra-articular ligament length measurement “y” and ACL inclination angle measurement “z”. Oblique (in the same plane as the ACL runs) coronal cuts showing a complete ACL tear with separate images of a PL bundle tear (D) and an AM bundle tear (E).

assessing concomitant injuries and presurgical planning in general (Fig. 43-11).

Reconstruction is performed with use of a tendon-graft that will replace the native ACL. Commonly used graft sources are the patellar tendon, the hamstrings and the quadriceps tendon. These tendons can be harvested from the same knee (i.e., autografts), during the same procedure. Alternatively a donor graft (i.e., allograft) can be used. Both have their own subset of pros and cons, with the most important pro being absence of donor-site morbidity for allograft and better healing potential for autograft.

Injuries of the PCL are less common than other knee ligament injuries. Frequently seen causes are a bent knee hitting a dashboard in a car accident or falling on a knee that is bent during running. A rupture of the PCL is usually better tolerated than ACL rupture, since many tears (i.e., grade I and II) have the potential to heal on their own and do not result in much knee stability problems. Most Grade I and II injuries are treated nonoperatively. Combined PCL/PLC and PCL/MCL and Grade III PCL injuries however, do present a challenge with regard to management decision-making. Chronic PCL-deficient (Grade III) knees have an increased incidence of osteoarthritis, particularly in the patellofemoral and medial knee compartments. Indication for surgery is influence by age, activity level, and presence of concomitant injuries. Different surgical techniques have been proposed; the most common are the “inlay” technique and the transtibial technique.

The goal of cruciate ligament (both ACL and PCL) reconstruction is to restore native knee kinematics, to provide the patient with the best potential for a successful outcome and to prevent from the development of long-term complications, such as osteoarthritis.

Posterolateral Corner

Critical structures of the posterolateral corner (PLC) are the LCL, popliteus tendon and popliteofibular ligament. These structures each contribute to the static and dynamic stability of the knee and are commonly injured concomitant with other ligamentous injury, mostly together with the torn ACL.³⁸ The importance of closely evaluating the PLC after knee injury is demonstrated by the fact that a deficient PLC causes altered

knee biomechanics and subsequently increases stress on surrounding stabilizing structures. As such, it has been shown that a deficient PLC is a primary cause of cruciate ligament reconstruction failure.

Acute high-grade injuries of the PLC with obvious deficient structures require surgical intervention. Since primary repair becomes increasingly difficult as time between injury and surgery increases, a cut-off of 2 to 3 weeks is usual to either repair or reconstruct the deficient structures. With more chronic PLC injuries, reconstruction is recommended to restore knee stability.

HIP

Femoroacetabular Impingement

Femoroacetabular impingement (FAI) is a pathologic condition that refers to impingement of the anterior femoral head-neck junction against the anterosuperior labrum. This is frequently caused by abnormal bony offset at the femoral head-neck junction, abnormal acetabular anteversion or excessive anterolateral acetabular bony rim coverage (Pincer lesion), and combined CAM-Pincer lesions. Recognition of FAI can be clinically and radiologically difficult. However, familiarity with this disorder is essential, as FAI can lead to labral tears, cartilage delamination, and if untreated, osteoarthritis.

Commonly, patients present with anterior groin pain exacerbated by activities involving hip flexion or pain over the greater trochanter as well as grinding or popping. Patients report pain with flexion and internal rotation and after prolonged sitting. On examination, there is a decrease in internal rotation that appears out of proportion to the loss of the other ranges of motion and there is limited flexion. The impingement test, elicited by 90 degrees of flexion, adduction and internal rotation of the hip, is almost always positive.

The imaging findings of FAI can be seen on plain radiographs, CT scan, MRI, and MRA. Some of the abnormalities seen include abnormal lateral femoral head/neck offset seen as a lateral femoral neck bump, os acetabulae, synovial herniation pits, acetabular over-coverage, hyaline cartilage abnormalities, and labral tears.

Treatment of FAI has traditionally been surgical and has come from open surgical treatment with open acetabuloplasty, and later open procedures through a transtrochanteric approach and combined open-arthroscopy assisted techniques to full arthroscopic approaches. Hip arthroscopy is becoming increasingly popular and being more frequently applied for this indication. This popularity is largely the result of studies reporting on improvement of functional outcome measures with follow-up up to 10 years, with low complication rates in several large study populations.

SPINE

Spinal Trauma

In spinal injury spinal stability must be assessed, and the patient immobilized until his spine is cleared. CT scan is more reliable in assessing spine injury than plain radiographs. When neurologic deficits are present a decompressive procedure may be indicated. In spinal cord compression, prompt decompression should be performed. Animal models of spinal cord injury suggest that prompt decompression can lead to objective improvement of recovery. Spinal cord injuries should be triaged to trauma centers since trauma center care is associated with reduced paralysis.

Occipital Cervical Dislocation

Motor vehicle accidents can cause dislocation of the occiput on the condyles of the atlas (C1). Most patients with this injury suffer cervical cord injury, and do not survive. Traction on the spine is contraindicated. Treatment consists of stabilization and fusion in situ using a screw plate from the mid cervical spine to the occiput.

Fractures of C1 (Jefferson Fracture)

Fracture of the C1 ring was described by Jefferson in 1920. The thin anterior and posterior rings of the C1 vertebra fracture with axial loads. C1 fracture causes the lateral masses of C1 to spread, which is visible on a through-the-mouth AP X-Ray image of the cervical spine. This injury is rarely associated with neurologic injury. Bracing with a cervicothoracic orthosis or a halo ring and vest is the recommended treatment for a Jefferson fracture.

Fractures of C2 (Odontoid Fracture)

Half of normal cervical rotation occurs at the atlanto-axial joint. The odontoid (Dens) is a small bony process which arises from the body of C2, and articulates with the body of C1 (the Atlas). Odontoid fractures are most often type I fractures (an avulsion fracture off the tip of the dens). Type I fractures occur when there is tension applied to the alar ligaments (which span from the tip of the odontoid to the skull bypassing the C1 vertebra). Type I fractures are stable and managed nonoperatively.

A type II fracture, at the base of the odontoid, results from lateral loading forces. Operative stabilization is the preferred treatment since immobilization in a halo vest results in non-union rates ranging from 20% to 80%. Transfixing the odontoid fracture with a screw maintains rotational movement. Posterior fusion of C1 on C2 with sublaminar wiring resulting in decreased range of motion is another option.

Type III fractures extend into the body of C2, below the origin of the odontoid process. Type III fractures are generally treated with halo brace. (Anderson and D'Alonzo)

Hangman's Fractures of C2

Hangman's fractures result from sudden extension forces on the neck and occur between the superior and inferior facets (pars interarticularis) of C2. Treatment is simple immobilization in a halo vest. Higher energy injuries causing severe extension forces can dislocate the C2-3 facet complex and damage the C2-3 disc. Such fractures can compromise the spinal canal, and death can occur from compromise of respiration. Significantly displaced Hangman's fractures are managed by internal fixation and bone grafting between C2 and C3.

Compression Fracture of the Cervical Spine

In C3 to C7 an axial load can cause fracture of the endplate while preserving the posterior cortex of the vertebral body. These fractures generally heal well, and are treated nonoperatively with analgesics and a cervical brace.

Burst Fractures of the Cervical Spine

Diving accidents are the classic cause of *Burst fractures* of the cervical spine. The axial load when an unrestrained passenger in an automobile accident strikes the windshield the posterior cortex of the vertebral body fractures leading to displacement of bony fragments into the canal injuring the spinal cord. Burst fractures are treated surgically by anterior debridement of the fracture and reconstruction using a bone graft strut stabilized with a plate and screws.

Unilateral and Bilateral Facet Dislocation

Another injury associated with motor vehicle accidents is facet dislocation. A restrained passenger can suffer forced flexion with distraction resulting in dislocation of the facets. The diagnosis can be made on lateral radiographs. Treatment consists of axial traction with cranial tongs, graduated application of weight, and periodic X-Rays. The patient is kept awake for safety concerns. When reduction is attained, patients are taken to surgery for posterior fusion with interspinous process wiring or a screw plate.

Clay-Shoveler's Injury

Clay-Shoveler's injury can result from a motor vehicle accident or from shoveling soil or clay. The injury (of C6, C7, T1, and T2) is the result of avulsion fracture of the spinous process by the paraspinal muscle forces. The fracture is treated nonoperatively with analgesics and a soft collar.

FRACTURES OF THE THORACIC AND LUMBAR SPINE

Thoracic Lumbar Spine Injury

The ribs stabilize fractures of the thoracic spine, making these fractures more stable than similar fractures of the lumbar spine. Neurologic injuries are more common in the thoracic and proximal lumbar spine because of the presence of the spinal cord, which ends at the L2 level.

Compression Fracture

Compression fractures result from osteoporosis and abnormal bone density as well as trauma. Compression fractures involve a fracture of the superior or inferior endplate without associated posterior cortex fracture. Thoracolumbar compression fractures are treated nonoperatively with braces and analgesics.

Burst Fracture

Burst fractures are caused by falls and high energy automobile accidents. One or both endplates and the anterior cortex of the vertebrae with an associated fracture of the posterior cortex. The posterior cortex fracture differentiates the burst fracture from a compression fracture and results in retropulsion of bone into the canal, which can cause nerve injury. A vertical lamina fracture may contain an invaginated segment of the dura mater with accompanying nerve roots, and posterior surgery can result in dural tear or nerve injury.

If nerve injury is noted, treatment is an anterior exposure and removal of the fractured anterior elements (corpectomy) and a strut graft is placed. A laterally placed plate and screws add stability to the construct.

Seatbelt Injuries (Flexion Distraction Injuries)

A seatbelt injury occurs when there is acute forward flexion of the trunk and anterior (i.e. seatbelt) restraint. The pelvis and upper torso move forward, and failure of the spine under tension begins with the posterior elements. Tearing of the dorsal fascia, the interspinous ligament, dislocation of the facets, and tearing of the discs occurs. The bone of the spinous process, the lamina, the pedicles, and the vertebral body fail in tension ("Chance Fracture").

In flexion distraction injuries through soft tissue, posterior internal fixation and bone graft is recommended. "Chance fractures" are treated with bracing.

Fracture Dislocations of the Spine

Fracture dislocations of the spine displace the bony elements by translation or rotation resulting in canal narrowing and nerve injury.

Reduction of the displaced bones is the best way to improve the canal dimensions.

Patients with fracture dislocations of the spine and partial nerve function can recover. Fracture dislocations are treated operatively with surgical stabilization.

Disc Herniation

Disc herniation, most common between ages of 20 and 50, can occur in the cervical, thoracic, or the lumbar spine, and consists of a tear of the annulus allowing the nucleus pulposus material to extrude through the annulus and enter the canal, pressing on the exiting nerve or the 'traversing' nerve roots. In the cervical spine, spinal cord compression can occur.

Symptoms of most disc herniations resolve within eight weeks as the nerve root accommodates and inflammation recedes. The bulk of the extruded nucleus pulposus resorbs over time. When symptoms persist beyond six to eight weeks, excision of the involved disc and decompression of the nerve roots may be indicated.

In cervical disc herniation an anterior approach to the spine is performed with dissection through a transverse incision on the neck. Dissection is carried between the trachea and the carotid sheath. The disc is then removed. The disc space may be bone grafted to fuse the vertebrae. A locking screw low profile titanium plate is then attached to the vertebrae.

Posterior decompression and laminectomy exposes the posterior elements of the spine. A portion of the lamina is removed to allow access to the canal to correct foraminal impingement or to remove lateral disc herniations. While the posterior approach

does not require fusion with plates and screws, central disc herniation cannot be managed through a posterior approach since the spinal cord cannot be safely retracted.

For lumbar disc herniation a midline incision is used and laminectomy allows visualization of the lateral recess. Retraction of the dura allows visualization of the traversing nerve roots as well as of the disc fragment.

Spinal Stenosis

A loss of hydration of the discs causes loss of disc height and bulging of annular tissue and the ligamentum flavum which effectively narrows the canal (spinal stenosis). Osteophyte formation on the facet joints can also cause nerve impingement. Cervical stenosis can cause myelopathic symptoms (hyperreflexia, ataxia, balance problems, weakness, and pain).

Lumbar stenosis causes neurogenic claudication (progressive pain, weakness, and numbness in the legs). The claudication symptoms result from standing and walking which increases lumbar lordosis. The symptoms resolve with sitting and bending forward (decreasing lumbar lordosis).

Spinal stenosis is treated with epidural steroid injections and physical therapy. Resistant cases may require surgical decompression and stabilization with plates and screws.

Spinal stenosis usually occurs in patients over 50 years of age. With degenerative spondylolisthesis or scoliosis fusion procedures with instrumentation may be required to prevent progression of the deformity.

Back Pain and Degenerative Disc Disease

Back pain occurs in the majority of adults but is usually self-limited resolving in one to two weeks. Chronic unremitting back pain suggests the possibility of infection, malignancy, or metastatic disease.

While radiographs are one option in the management of disabling low back pain, they are ineffective at ruling out malignancy, and radiographic findings correlate poorly with symptoms. Patients with severe degenerative symptoms may have no pain, while others with mild degenerative findings complain of severe pain. The potential for secondary gain and psychiatric problems and the unpredictable results of spine fusion add to the difficulty of diagnosis and choosing a treatment plan.

Intervertebral disc replacement prostheses are now used to treat degenerative disc disease. The potential for loosening, creation of wear debris, and bone loss complicating revision surgery are concerns, as are the proximity of the device to the spinal canal and the great vessels.

Scoliosis

Scoliosis is a lateral curvature of the spine. Lateral bending of the spine is always accompanied by rotational deformity (coupling).

In order to measure the severity of scoliosis lines are drawn along the endplates of the vertebral bodies at either end of the curve and the angle formed when these lines intersect is magnitude of the curve.

Scoliotic curves are classified as congenital, degenerative, metabolic (mucopolysaccharidoses), neurogenic (cerebral palsy), and myogenic curves (muscular dystrophy). Idiopathic scoliosis is the most common form, and represents a spectrum of genetic disease.

Adults with scoliosis may present with axial pain and imbalance in posture. Treatment for scoliosis may include medications, therapy, and activity modification. In severe cases with objective deformity surgical correction of the deformity may be indicated.

Idiopathic Scoliosis

The majority of idiopathic scoliosis curves become apparent during adolescence and progress during skeletal growth. Initial management consists of observation. Rapidly progressing curves are treated with braces. Brace treatment is recommended for curves between 20 and 40 degrees. For patients with large curves, surgical intervention may be needed using rods with grafting and fusion.

Neuromuscular Scoliosis

Neurologic conditions such as polio and cerebral palsy can lead to ‘uncompensated’ scoliosis curves where the patient is unable to lean with his upper body to restore balance. Scoliosis correction surgery may be needed to facilitate sitting balance, and to avoid skin breakdown caused by pelvic obliquity.

JOINT RECONSTRUCTION

Introduction to Arthritis

Arthritis refers to a large number of medical conditions, including osteoarthritis, rheumatoid arthritis, septic arthritis, and post-traumatic arthritis. Each has the potential to lead to loss of articular cartilage lining the joints. According to the CDC and the National Health Interview Survey approximately 50 million adults (22% of the U.S. population) have been diagnosed with some form of arthritis. This number is projected to grow to an astounding 67 million adults by 2030 (or 25% of the U.S. population).

The number of individuals suffering from arthritic conditions will continue to rise as the ‘baby boomer’ generation enters old age and with the rise in obesity in the U.S. population, as age and obesity are two major factors in the onset of arthritis.

Conservative Management and Prevention of Arthritis

Conservative measures to treat arthritis include weight loss, activity modification, rest, bracing, physical therapy, pain management, and assistive devices such as canes or walkers. Conservative measures have the potential to decrease symptoms and improve function and quality of life. These measures can successfully manage a patient’s condition and avoid a surgical procedure. Osteoarthritis symptoms tend to be intermittent in nature or associated with high impact activities. Initially treat all patients with conservative measures and avoid surgery if possible.

Conservative measures can also play a role in the prevention of arthritis. Weight loss of as little as 11 pounds has been shown to decrease the risk of developing knee osteoarthritis in women by 50%. Similarly, patients who engage in regular physical activity have been found to have lower incidence of arthritis.

Arthritis causes pain, loss of range of motion, decreased ability to perform work duties or participate in social functions, and decreased quality of life. Despite conservative therapy, frequently more invasive treatments are needed to effectively manage the patient’s symptoms.

Examination of the Patient

A thorough history and physical examination (H&P) is indicated for all orthopedic patients. Patient history should include location, quality, severity, timing, and radiation of pain along with any referred pain, associated signs and symptoms, modifying

factors, prior treatments, including both conservative and surgical treatments. Other details within the H&P are equally important for diagnostic purposes and to successfully develop a treatment plan. If you listen carefully to your patient, they will often tell you their diagnosis. Location of “hip pain” can narrow a differential diagnosis. Patients with activity related groin pain often are found to have hip arthritis, whereas patients with peri-trochanteric pain (lateral hip pain) may be suffering from trochanteric bursitis. The importance of listening and focusing on the patient’s description of location and type of pain cannot be overemphasized.

Physical examination should begin by observing the patient’s gait, both with and without assistive devices if possible. This demonstrates how significantly the patient is affected functionally and the effect of the patient’s pain. Typical gait patterns include a “Trendelenburg gait” where abductor weakness may lead to a poor outcome following total hip arthroplasty. Other aspects of the exam include assessment for leg length discrepancy, joint contractures, skin changes, assessment for prior surgical incisions to evaluate for prior treatments or to plan future surgical approaches, neurovascular examination, strength and range of motion. These details document functional status and help to formulate a differential diagnosis. Patients with ‘hip pain’ may have lumbar spinal stenosis, radiculopathy, or vascular disease that may be playing a large role in their presentation. Once an appropriate physical examination is complete, weight-bearing radiographs are needed. Advanced imaging, including CT and MRI are rarely indicated in initial work up of patients. Once a diagnosis is made, specific treatment directed towards the patient’s condition can be initiated. The goals of treatment are to improve pain, preserve motion and to maximize patient function, independence, and quality of life.

Injections

Joint injections are commonly performed into the knee and shoulder. Common injections into the knee include corticosteroids and Hyaluronic-acid gels. Corticosteroid injections can decrease inflammation within the joint. These injections are usually administered in combination with a local anesthetic, such as Lidocaine, in order to provide more immediate relief for both diagnostic and therapeutic purposes. If the patient has immediate relief of their pain symptoms with injection of the joint, this localizes the source of the patient’s pain to the joint and may assist with diagnosis. At the same time any benefit received is therapeutic for the patient. Hyaluronic acid injections have become popular and are commonly referred to as “*viscosupplementation*.” The exact mechanism of these injections is not known, however patients may benefit from these injections by increasing the viscosity of the synovial fluid. The injections do not lead to articular cartilage repair. There is a risk of joint infection, cartilage injury from the needle, hemarthrosis, and failure to receive benefit. A theoretical risk of altered glucose metabolism in diabetics also exists with corticosteroid injections.

Surgical Management of Arthritis

The most commonly performed procedure for arthritis of a major joint is arthroplasty, or joint replacement. Joint replacements, including hip and knee arthroplasty are considered two of the most successful procedures performed in all of surgery. However, other nonarthroplasty options exist. These are typically performed for specific diagnoses under specific indications.

Osteotomy. Osteotomy is cutting the bone to change the position of the fragments in order to improve length, rotation, alignment, or angulation. Osteotomy can be performed for both congenital and acquired deformities that are thought to be contributing to the patient's pain or development or progression of disease. Pelvic and femoral osteotomy can be utilized in treatment of developmental dysplasia of the hip. With this procedure the position of the acetabulum can be altered in order to provide more appropriate coverage of the femoral head, which is usually deficient anteriorly and laterally. Femoral osteotomies can also be performed to correct anteversion and varus/valgus deformity of the femoral neck. Osteotomies are performed to obtain more normal alignment and coverage of the femoral head within the acetabulum to prevent or delay future disease.

An osteotomy commonly used in the knee is a proximal tibia osteotomy. An adult patient who presents with isolated medial compartment knee arthritis and associated varus deformity would be an ideal candidate for valgus (high tibial) osteotomy. An osteotomy that realigns the knee into slight valgus has the potential to off-load the medial compartment, slow disease progression and prevent or delay the need for more invasive procedures (unicompartmental or total knee arthroplasties).

Arthrodesis. Arthrodesis is a treatment option for severe arthritis where the overlying articular cartilage is removed and the two opposing bones are allowed to heal together. After successful arthrodesis no motion is possible through the joint and the source of pain is removed. Arthrodesis of large joints, such as the knee, shoulder or hip, are typically explored as an option in the face of infection, in elderly, low demand patients or in young and active patients who are considered too young for a joint replacement (concern for component wear and need for early revision). Arthrodesis can also serve as a "last resort" procedure in orthopedics, when joint preserving treatments fail, fracture, infection, etc. Arthrodesis requires removal of overlying articular cartilage from bone and frequently the use of autograft or allograft bone and the use of hardware for internal fixation or temporary external fixation.

Joint Arthroplasty/Joint Replacement. Joint arthroplasty is considered the final option for patients suffering from pain associated with arthritis in the joint. The surfaces of the bones are replaced after removing the damaged articular cartilage. The amount of bone and the determination of how to make the bone cuts is made based on pre-operative radiographs and templating, cutting guides, computer navigation, and anatomic measurements. The cut bony surfaces are covered with new components, usually made of metal, ceramic, or polyethylene. These new components are sized to appropriately match the patient, based on templating pre-operative radiographs, intra-operative measurements, and examination for stability, leg length, alignment, and range of motion.

If all compartments or surfaces of the joint are replaced, the arthroplasty is referred to as a total joint arthroplasty. In comparison, if only one surface or compartment of the joint is replaced, it is referred to as hemiarthroplasty (hip, shoulder) or unicompartmental arthroplasty (knee). Total hip and knee arthroplasties are considered the most successful of all surgical procedures performed in terms of patient outcome and improvement in pain.

Hip Arthroplasty

Background Hip arthroplasty is utilized for end stage arthritis in the hip that has failed a reasonable trial of non-operative measures (Fig. 43-12). Conventional hip arthroplasty commonly refers to *total hip arthroplasty* where both the femoral

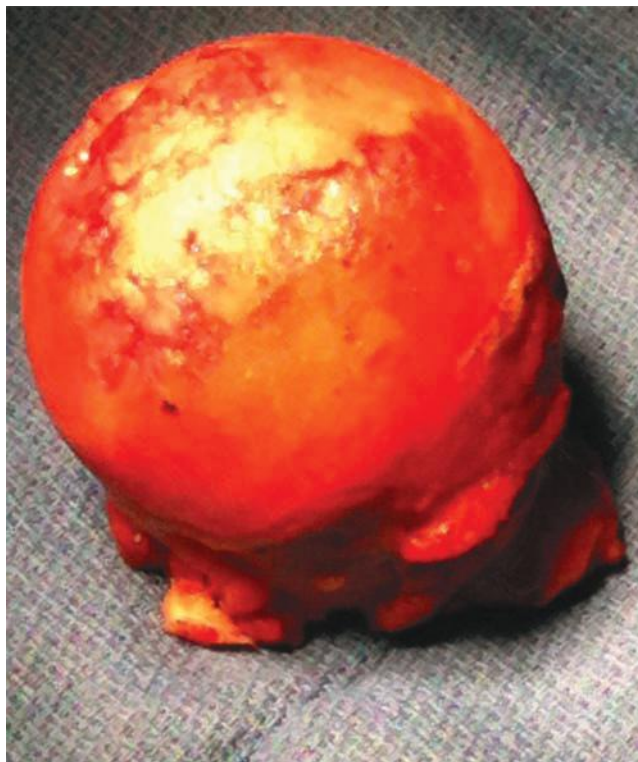


Figure 43-12. Osteoarthritis femoral head. Note erosion of weight-bearing cartilage and peripheral osteophytes.

head and neck are replaced. Hip resurfacing is a form of hip arthroplasty, used in younger patients with end stage arthritis. Resurfacing of the femoral head is performed with a metal cap (without performing a femoral neck cut and placing a stemmed femoral component) and the acetabular surface is replaced with a metal cup. Resurfacing functionally achieves the same result as a total hip arthroplasty, however it preserves femoral bone for later conversion to total hip arthroplasty if necessary. Finally, hemiarthroplasty describes the replacement of the femoral head and neck with a stemmed femoral component in isolation. The acetabulum is not addressed surgically.

History of Hip Arthroplasty The history of hip arthroplasty (hip replacement) may be broken down into a "Pre-Charnley" era and a "Post-Charnley" era, referring to the significant contributions of Sir John Charnley to the evolution of hip arthroplasty. Prior to Charnley's contributions, hip arthroplasty consisted of a variety of procedures with highly variable results. Early attempts at relieving hip pain were made with interpositional arthroplasty, where tissue layers, plastic, or metal were placed between the worn articular surfaces. Fracture of the interposed material or loosening of components often led to failure.

Later attempts introduced stemmed components to improve fixation. One of the earliest femoral components was designed by Austin-Moore. This prosthesis replaced the femoral head and neck with a metal component secured into the femoral shaft with a stem extending down the diaphysis. This prosthesis was utilized in hemiarthroplasty for many years and served as a step in the development of total hip arthroplasty with the later addition of the acetabular component.

Surgical Approaches to the Hip A variety of approaches to the hip joint have been utilized in joint arthroplasty, including anterior approach (Smith Petersen), anterolateral approach

(Watson-Jones), lateral approach (Hardinge), and posterior approach (Kocher Langenbach). Each approach contains a unique set of advantages and disadvantages. Below, a comparison of the anterior and posterior approaches is made.

Anterior approach (Smith Petersen)—This approach utilizes the internervous plane between the femoral nerve and superior gluteal nerve. Superficially, the plane between the sartorius (femoral nerve) and tensor fasciae lata (superior gluteal nerve) is dissected, while deep, the plane between the rectus femoris (femoral nerve) and gluteus minimus (superior gluteal nerve) is dissected. The anterior approach to the hip is a “muscle sparing approach” and theoretically leads to less muscle damage and functional loss. Measuring serum CK values, the level of CK found with a posterior approach is nearly 2 times the value found in comparison to that seen with an anterior approach to the hip. Other advantages to this approach include low dislocation rates, decreased postoperative restrictions, and excellent acetabular exposure. Downsides include difficult preparation and placement of the femoral component and lack of a true extensile approach.

Posterior approach (Kocher Langenbach)—In comparison to the anterior approach, the posterior approach is a muscle splitting approach. In addition, there is no true internervous plane. After incising the skin and subcutaneous fat, the fascia lata is incised along with the gluteus maximus in line with the skin incision. The short external rotators are exposed and dissected, including the piriformis, superior and inferior gemelli, obturator internus and externus, and quadratus femoris. This allows internal rotation of the hip along with flexion and adduction to dislocate the femoral head for exposure. The posterior approach has an increased risk of post-operative dislocation, however this is minimized if soft tissue repair is performed. Postoperatively patients are required to follow strict hip precautions to minimize risk of dislocations; avoiding placing the hip in excessive flexion, adduction, and internal rotation (“The Heisman pose”). The posterior approach is extensile and provides excellent exposure of both the femur and acetabulum for complex and revision cases.

Minimally invasive total hip arthroplasty has been advocated in recent years. Theoretical benefits include improved cosmesis, decreased soft tissue damage, and decreased blood loss, quicker postoperative recovery and a shorter hospital stay. However, smaller incisions come with the disadvantage of decreased

12► visualization intra-operatively and associated risks of component malposition, intraoperative fracture, and nerve or vascular injury. In fact, the only documented benefit of minimally invasive techniques appears to be improved cosmesis.

A greater trochanteric osteotomy can be performed in order to mobilize the abductors. This can improve exposure to the acetabulum and femur and can be useful particularly in revision cases.

Bearing Surfaces in Hip Arthroplasty The most common combination of bearing surfaces used in total hip arthroplasty is a metal femoral head (generally cobalt chrome), articulating with a polyethylene liner. Ceramic and metal are alternative bearing surfaces commonly utilized in total hip arthroplasty, either used in combination with a polyethylene acetabular liner (ceramic on poly or metal on poly) or in metal on metal and ceramic on

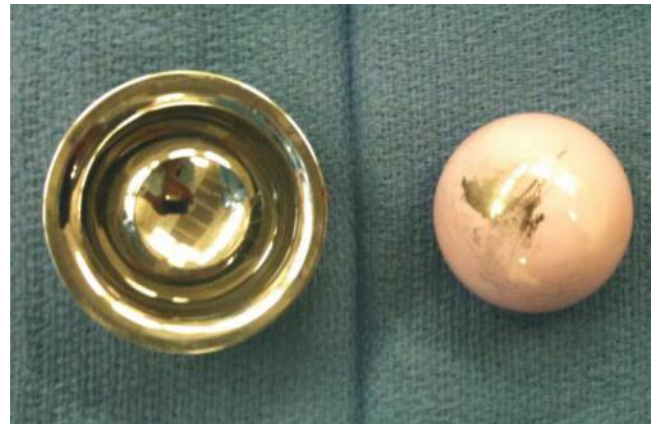


Figure 43-13. Failed ceramic on metal hip arthroplasty components. Note the metallic staining on the ceramic femoral head.

ceramic articulations. Metal on metal and ceramic on ceramic articulations have the advantage of lower friction and decreased wear rates in comparison to metal on polyethylene articulations. Metal on metal articulation is utilized commonly in hip resurfacing, however its use in total hip arthroplasty is controversial. Metal on metal articulation has many advantages, including lower wear rates and decreased associated osteolysis. The surgeon also has the ability to use a larger femoral head, thus achieving a greater femoral head to neck ratio and providing the patient a greater arc of motion prior to impingement and subsequent dislocation. Metal on metal (MOM) articulations have been associated with production of metal ions, pseudotumors, hypersensitivity reactions, and early failure when used in total hip arthroplasty (Fig. 43-13). Metal ions pose a theoretic risk of causing problems with pregnancy or a theoretic risk of cancer. Studies have failed to demonstrate a statistical increase in cancer in patients who have MOM articulations in comparison to metal on poly articulations. Ceramic on ceramic articulations have the lowest wear rate and friction of all current bearing combinations. However, ceramic has poor mechanical properties and can lead to component fracture due to its comparatively brittle nature.

Alignment of Hip Arthroplasty Components Proper alignment of hip arthroplasty components is vital to a successful procedure and patient outcome. Surgeons aim for appropriate alignment of components to restore a functional and stable range of motion. This is accomplished with combined anteversion of the femoral and acetabular components, appropriate abduction of the acetabulum and focus on staying true to Sir John Charnley’s principles: establishing a low friction articulation, medializing the acetabular component and center of rotation and restoring abductor length and tension with restoration of appropriate length and femoral offset. Inappropriate placement of components can lead to early failure, accelerated component wear, dislocation, need for revision surgery and poor patient outcome and satisfaction.

Knee Arthroplasty

Background Knee Arthroplasty is indicated for end stage arthritis within the knee that has failed to respond to a reasonable trial of non-operative and conservative measures. (Figs. 43-14 and 43-15) Knee arthroplasty commonly refers to total knee arthroplasty where the distal femur, tibia, and patella are resurfaced after any remaining articular cartilage and a layer of subchondral bone are resected. A unicompartmental knee arthroplasty



Figure 43-14. Valgus deformity. Osteoarthritis of lateral compartment right knee.



Figure 43-15. Osteoarthritis of both knees. Note varus alignment of right knee, and valgus alignment of left knee (“windswept deformity”).

consists of replacing one compartment of the knee, most commonly the medial compartment, for unicompartmental disease. Similarly, isolated replacement of the patellofemoral joint can be performed for end stage patellofemoral arthritis

Surgical Approach to the Knee Total knee arthroplasty is generally accomplished through a medial parapatellar approach. This approach utilizes a longitudinal skin incision, usually midline over the patella, extending on average from 5 cm proximal to the patella to the tibial tubercle distally. Dissection is carried down to the capsule where a medial parapatellar arthrotomy is performed to gain access to the joint. This approach provides excellent exposure to all three compartments of the knee after patellar dislocation. On occasion, a lateral parapatellar arthrotomy is warranted and this can be performed safely. In the event that the patella does not dislocate, the arthrotomy can be extended proximally through the quadriceps. This has no effect on patient outcome.

Once the joint surfaces are adequately exposed, remaining articular cartilage and a thin layer of underlying bone are removed prior to placement of prosthetic components. Bone cuts are made based on pre-operative templating, cutting guides, computer navigation, and anatomic measurements (Figs. 43-16 and 43-17).

Bearing Surfaces in Knee Arthroplasty The femoral component consists of a metal prosthetic cap designed and sized to fit the normal shape of the femoral condyles. The tibia is cut perpendicular to the anatomic and mechanical axis and a flat, stemmed, metal tray is placed, which most often articulates with a polyethylene liner. The patella is resurfaced with a polyethylene component. Options exist for a mobile bearing



Figure 43-16. Standard total knee instruments.

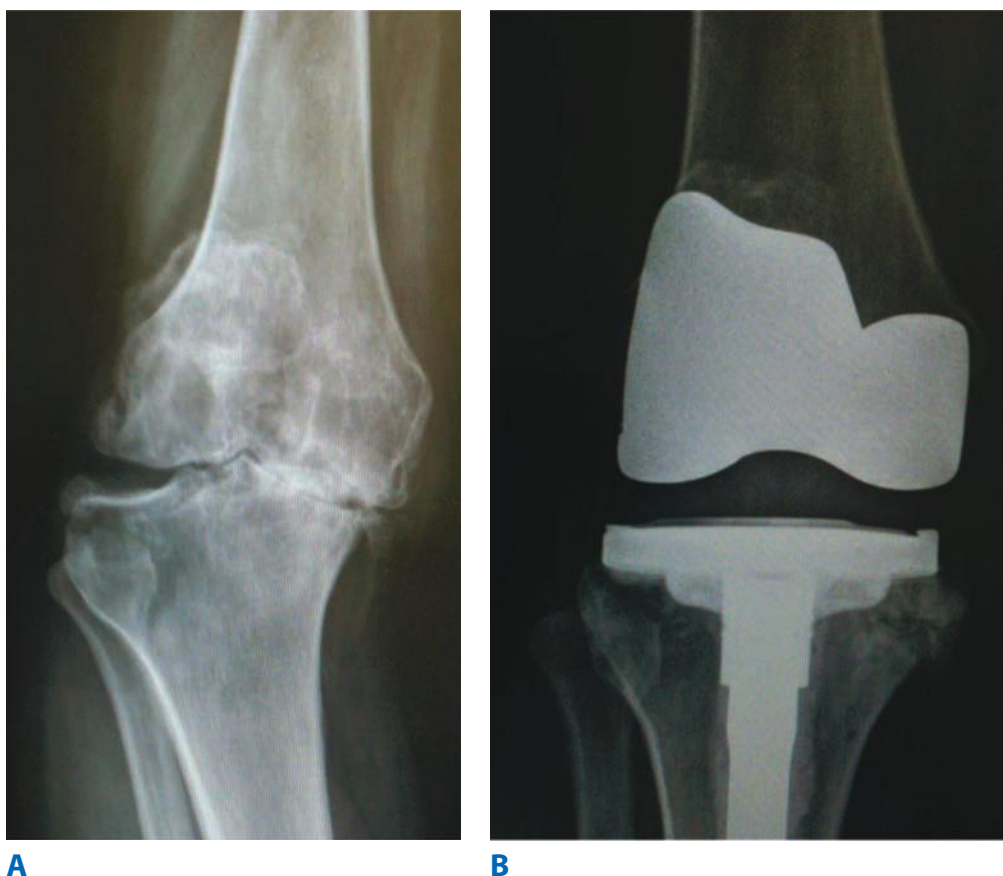


Figure 43-17. A. Varus knee with osteoarthritis. B. Right total knee replacement.

knee arthroplasty. With this design the polyethylene component is not fixed rigidly to the metal tibial tray and has the ability to more highly conform to the femoral component through the range of motion arc with designed ability for motion in its articulation with the tibial tray. Although excellent results have been published, this design has not been proven to lead to improved outcome or decreased component wear.

Two types of primary total knee arthroplasty systems exist, including cruciate retaining and posterior stabilized systems. As the name implies, with cruciate retaining systems, the posterior cruciate ligament (PCL) is retained in hopes of preserving more normal knee kinematics and femoral rollback with flexion, while in posterior stabilized systems the ligament is sacrificed and the components are designed to accommodate for the loss. These two systems have equivalent results in knee arthroplasty.

Alignment and Balancing in Knee Arthroplasty Appropriate alignment of the components and balancing of the flexion and extension gaps are essential for a successful result in knee arthroplasty. Inappropriate component position can lead to early wear and failure, knee instability, pain, and post-operative stiffness with poor range of motion. The surgeon must perform appropriate soft tissue balancing and bone cuts to accomplish this and subsequently must place the appropriate sized components, usually replacing the exact amount of bone and cartilage that was removed to create the articulation, and restore stability. The knee must be stable to varus and valgus stress at all points through the range of motion arc and still be able to attain a full range of motion arc from full extension to deep flexion.

Computer Navigation and Joint Arthroplasty

Computer navigated joint arthroplasty has the theoretical benefit of more accurate and consistent placement of arthroplasty components through intraoperative feedback to the surgeon regarding component position, planned bone cuts and alignment (Fig. 43-18). In theory this would lead to improved patient outcomes (Fig. 43-19A and B). Negatives include increased costs of the technology and prolonged operative times. Use of computer navigation in total joint arthroplasty has been shown to provide statistically significant improvement in accuracy of component placement. Use of computer navigation will likely increase in the future as technology continues to improve.

Fixation Options in Joint Arthroplasty

Components in hip and knee arthroplasty can be secured into position with cement or biologic fixation. The cement most commonly used is polymethylmethacrylate (PMMA). PMMA serves as a grout between the component and the bone surface. Components secured without cement are grit blasted or porous coated to allow bony ongrowth or ingrowth, respectively. Hydroxyapatite can also be utilized on the implant surfaces to promote bone ingrowth or ongrowth through osteoconductive properties. A majority of hip joint arthroplasty components are now secured without cement where initial fixation of components is accomplished through press fit techniques. In knee arthroplasty, cement utilization is generally preferred. In hip replacement patients where biologic fixation would be unreliable such as an elderly, osteoporotic patient, or patients with prior radiation, cement may be a better option. With revision total hip arthroplasty, cement fixation

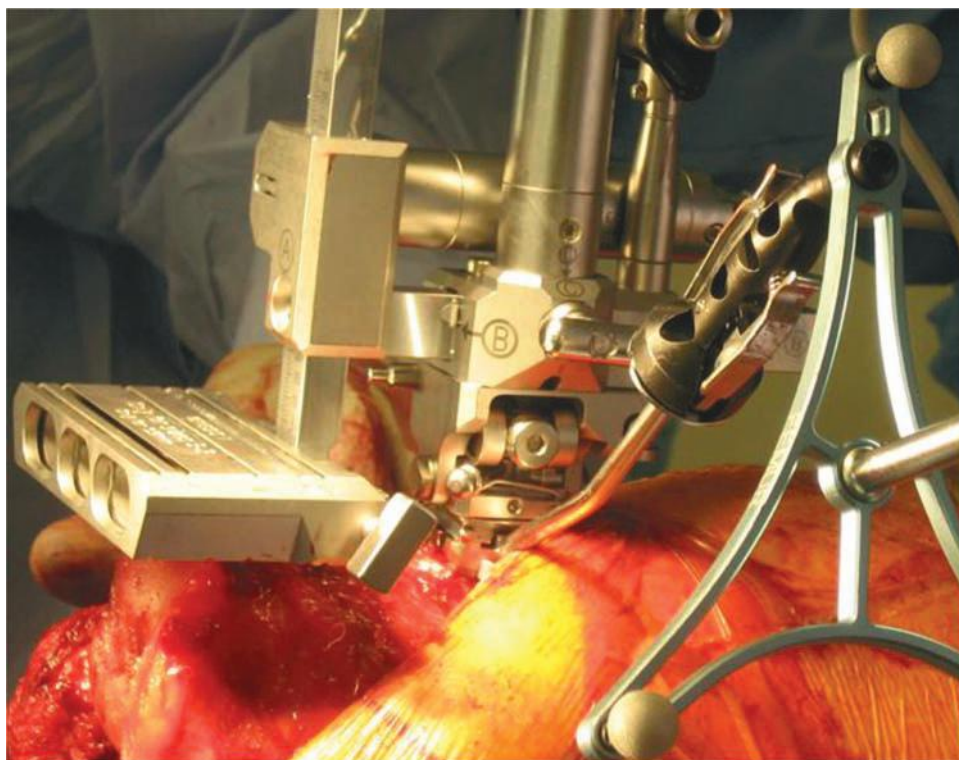


Figure 43-18 Computer assisted robotic targeting arm for total knee replacement.

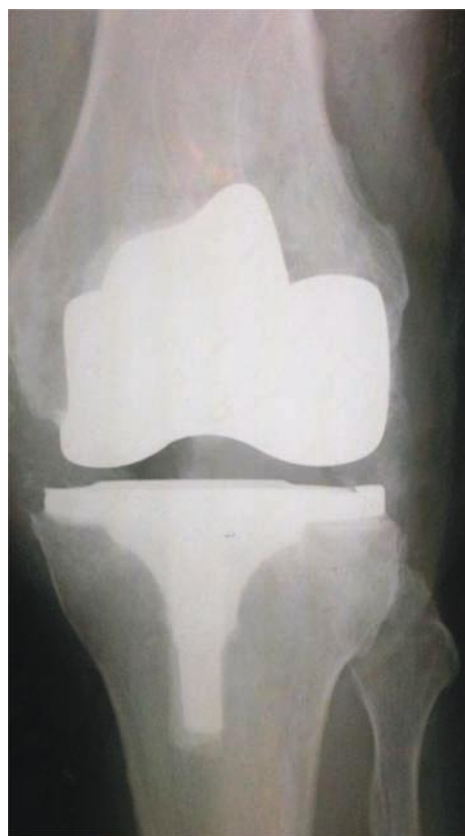
of components has been shown to lead to earlier mechanical failure.

Osteolysis and Aseptic loosening. Osteolysis is a term used to describe abnormal resorption of bone. Osteolysis can be caused by underlying infection, metastatic disease, or in

the case of joint replacement, the production of wear debris. Even with appropriately positioned components, some wear of the bearing surfaces is expected. However, the wear rates and the size and amount of wear debris with the different bearing surfaces can be quite different. The wear rate of ceramic



A



B

Figure 43-19. **A.** Valgus knee with osteoarthritis. **B.** Robotic assisted total knee.



Figure 43-20 Failed total knee replacement. Note subsided, loose, tibial component.

on ceramic articulations is the lowest of all bearing surfaces, however there is increased risk of component fracture and postoperative “squeaking.” In metal on polyethylene articulations, wear debris is produced and polyethylene particles are phagocytized by local macrophages. “Activated” macrophages lead to an osteolytic process and bone resorption. Particulate methylmethacrylate cement debris can also play a role in osteolysis. Improperly positioned components or patient related factors such as high impact activities can lead to a high wear rate. A substantial osteolytic response may occur and lead to component micromotion and aseptic loosening. Patients who present to clinic with pain following joint arthroplasty and an increasing zone of osteolysis in the periprosthetic region frequently need revision surgery (Fig. 43-20). Alternative bearing surfaces continue to be explored in hopes of decreasing or completely preventing wear of components and associated osteolysis and aseptic loosening.

Complications in Joint Arthroplasty. The risk of any complication following joint arthroplasty procedures falls in the range of 5% to 10%. Risks shared by hip and knee arthroplasties include infection, intra-operative or post-operative fracture, vascular injury with need of intra-operative or post-operative blood transfusion, nerve injury or nerve palsy (most commonly involving the deep peroneal nerve and loss of ankle dorsiflexion), periprosthetic fracture, stress shielding, component fracture or wear, and medical complications, including venous thromboembolic disease (DVT and PE), myocardial infarction, or cerebrovascular accident. Complications unique to total hip arthroplasty include dislocation, leg length discrepancy, iliopsoas impingement, or tendonitis.

Dislocation Following Hip Arthroplasty. Dislocation can result from malpositioned components (inadequate combined anteversion of the femoral neck and acetabulum, excessive ab- or adduction of the acetabular component), non-compliant patients, those with cognitive or neuromuscular disorders, inadequate soft tissue repair or excessive soft tissue loss from surgeries or revision surgery, fracture, improper restoration of length, and/or offset. Historically, there has been significant debate as to the role of the surgical approach and incidence of hip dislocation following hip arthroplasty. However, comparable dislocation rates have been found with anterolateral (0.70%), lateral (0.43%), and posterior with soft tissue repair (1.01%) approaches. Dislocation is often the result of poor patient compliance with post-operative restrictions, neuromuscular or cognitive conditions, or excessive soft tissue loss. History, physical examination and appropriate radiographs are vital to proper treatment of dislocation. Closed reduction can usually be performed with conscious sedation and gentle traction or manipulation. Rarely, open reduction may be necessary. Patients with multiple dislocations should be assessed for improperly positioned components. Patients with recurrent dislocations and improperly positioned components may need revision of the component. Patients with recurrent dislocations and properly positioned components should be considered for conversion to hemiarthroplasty or to a constrained total hip arthroplasty which provides improved stability.

ORTHOPEDIC PATHOLOGY AND ONCOLOGY

Diagnosis of Malignant Bone Tumors

History. Diagnosis of musculoskeletal tumors begins with a thorough patient history. A history of unremitting pain, unrelated to activity, or pain that interferes with sleep, suggests malignancy. Patient age can help in establishing a differential. Round blue cell lesions are most likely neuroblastoma in a five-year old, Ewing’s sarcoma in a 10-year old, lymphoma in a 20-year old, and myeloma in a 60-year old. Gender also adds information, for instance, giant cell tumor is more common in females, osteosarcoma in males. Multiple bone involvement may suggest fibrous dysplasia, enchondromas (Ollier disease, Maffucci’s syndrome), or osteochondromas (multiple hereditary exostoses).

Laboratory Test. Laboratory tests determine the level of cellular turnover (lactate dehydrogenase [LDH]) or of bone destruction (calcium, alkaline phosphatase). Elevated Prostate-specific antigen (PSA) suggests prostate cancer.

Imaging. Radiographic studies are critical to the diagnosis of bony tumors. Radiographs can help assess the aggressiveness of the tumor. Four questions should be addressed when assessing radiographs: (a) Where is the tumor—in which bone (Table 43-1) and in which part of the bone (Table 43-2)? (b) What is the tumor doing to the bone (clinical behavior)? (c) What is the bone doing to the tumor (biologic response)? (d) What is the matrix pattern? Matrix is the acellular interstitial substance produced by tumor cells. Particular attention should be paid to the junction between the tumor and the host bone since this margin can also indicate the aggressiveness of the tumor. Ewing’s sarcoma has a characteristic ‘onion skin’ periosteal reaction pattern. This reaction pattern also occurs in other tumors and infections.

Table 43-1

Common locations of bone tumors

FEMUR	
Distal posterior	Parosteal osteosarcoma
Distal anterior	Periosteal osteosarcoma, periosteal chondroma or chondrosarcoma, myositis ossificans
TIBIA	
Adamantinoma, chondromyxoid, Fibroma	
HANDS AND FEET	
Enchondroma, exostosis	
Calcaneus	Unicameral bone cyst, lipoma, chondroblastoma, osteosarcoma
SPINE	
Anterior	Metastatic, myeloma, Paget disease, vascular malformation, Giant Cell Tumor
Posterior	Osteoid osteoma, osteoblastoma; Aneurysmal Bone Cyst
PELVIS	
Metastatic, myeloma, chondrosarcoma, giant cell tumor, aneurysmal bone cyst, Paget disease, Ewing's Sarcoma	
SACRUM	
Chordoma (midline), chondrosarcoma, giant cell tumor, aneurysmal bone cyst, lymphoma	
RIBS	
Metastatic, myeloma, fibrous dysplasia, chondrosarcoma	

OSTEOSARCOMA

The most common primary malignant bone tumor is osteosarcoma (Fig. 43-21). Osteosarcomas are classified as osteoblastic, chondroblastic, fibroblastic, telangiectatic, round cell, and MFH-like, according to the predominant cell type. Most osteosarcomas present in patients between 10 and 20 years of age. Secondary osteosarcomas occur in older patients in abnormal bone affected by Paget's disease or radiation.

Table 43-2

Tumor location in bone**Epiphysis**

Chondroblastoma, clear cell chondrosarcoma, GCT, infection, dysplasia epiphysealis hemimelica (DEH)

Metaphysis

Most common site of involvement

Diaphysis

FEENOMASHIC: F-Fibrous dysplasia, EG-Eosinophilic Granuloma, N- NonOssifying Fibroma, O-Osteoid osteoma, M- Myeloma, A-Adamantinoma, S-Simple Bone Cyst, H-Histiocytosis, I-Infection

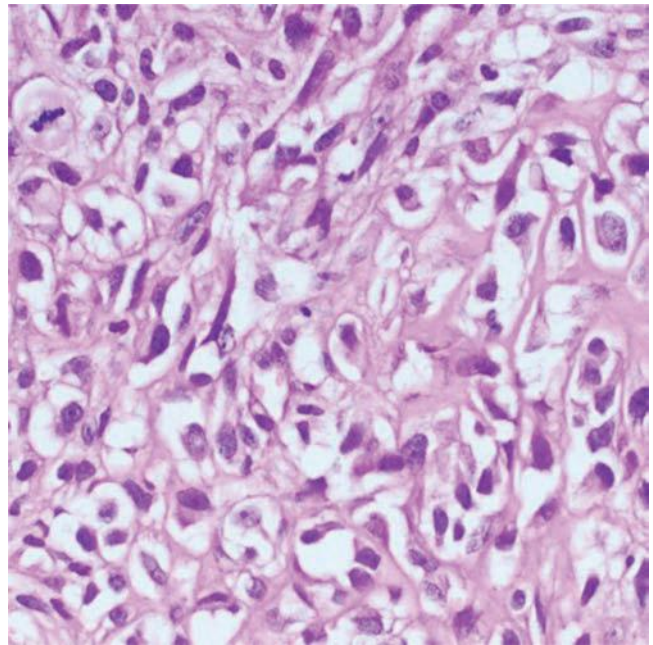


Figure 43-21. Osteosarcoma.

Parosteal Osteosarcoma

Parosteal osteosarcomas occur in women ages 20 to 50, “pasted on” the surface of the posterior distal femoral metaphysis. The preferred treatment is wide surgical excision.

Periosteal Osteosarcoma

Periosteal osteosarcoma occurs on the anterior surface of the distal femur or proximal tibia. The lesion appears chondroblastic on histology. Radiographs show scalloping of the underlying cortex with a ‘sunburst’ periosteal reaction. Treatment is wide surgical excision.

Paget's Sarcoma

Paget's sarcoma is a rare complication of Paget's disease. In Paget's disease with multiple bone involvement, osteogenic sarcoma, fibrosarcoma, chondrosarcoma, and MFH have occurred, most often in the pelvis, but also in the humerus, femur, spine, and skull. Imaging may demonstrate osteolytic areas, and loss of normal fatty marrow and multifocal lesions. Treatment of Paget's sarcoma is surgical excision, but the prognosis is poor.

Radiation-Induced Sarcoma

The three criteria for diagnosis sarcoma of radiation induced sarcoma are: (a) histology different from the original lesion, (b) sarcoma develops in the irradiated field, and (c) 3 to 5 year latent period between radiation and sarcoma development. Radiation for carcinoma of the breast and cervix can result in osteosarcoma, chondrosarcoma, fibrosarcoma, or MFH. Treatment is a combination of chemotherapy and surgery.

EWING'S SARCOMA

Ewing's sarcoma is the second most common primary bone tumor in patients under 30. The typical presentation is a tumor in the diaphysis of the femur in a young white male.

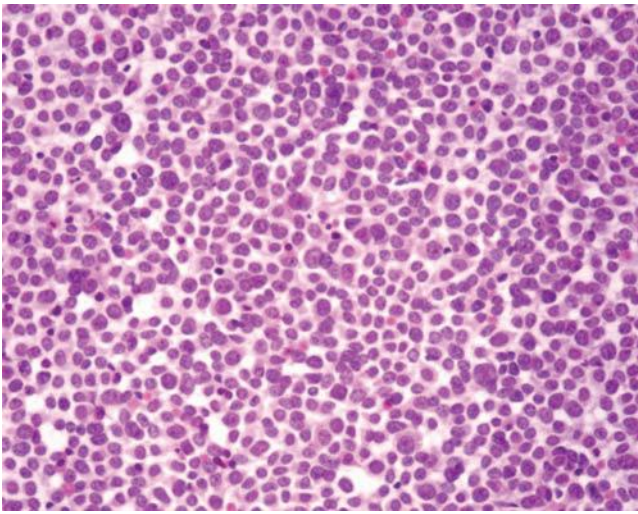


Figure 43-22. Ewing's sarcoma.

An “onion skin” periosteal reaction may be seen on radiographs. A large soft-tissue extension from the primary bone tumor may be seen and histology reveals a small round blue cell tumor (Fig. 43-22). Diagnosis is confirmed with bone marrow biopsy specimen. Bone scan can identify multiple lesions. Treatment is chemotherapy and surgery or radiation therapy for spine or pelvic lesions.

CARTILAGE FORMING TUMORS

Chondrosarcomas

Chondrosarcomas typically occur in male patients over 40 years of age, and are the third most common primary bone malignancies. Primary chondrosarcomas can form clear cell, mesenchymal, or dedifferentiated neoplastic cartilage. Secondary chondrosarcomas may also develop in pre-existing lesions such as exostoses or enchondromas. Pelvis, shoulder, and ribs are frequent locations. Chondroid or “popcorn” calcifications are typical on radiographs. Clear cell chondrosarcoma and mesenchymal chondrosarcoma occur in younger patients (second to fifth decades of life). Clear cell chondrosarcomas are low-grade lesions that often affect the epiphyses.

The treatment of chondrosarcoma is surgical excision, since cells are not chemosensitive or radiosensitive. For high-grade lesions, wide or radical resection is recommended. Pelvic and scapular chondrosarcomas have a high recurrence rate and adjuvant chemotherapy does not improve survival rates.

FIBROUS LESIONS OF BONE

Desmoplastic Fibroma

Desmoplastic fibroma is a rare tumor occurring in the mandible, femur, pelvis, radius, or tibia in young adults. Radiographs show a metadiaphyseal “soap bubble” appearance and endosteal scalloping. Histology resembles desmoid tumors or fibromatosis. Recommended treatment is wide excision.

Malignant Fibrous Histiocytoma of Bone

MFH occurs in the metadiaphysis of long bones after conditions like nonossifying fibromas and bone infarcts. Radiographs typically show destructive lesions with soft-tissue extension.

Histology resembles osteosarcoma with fibroblasts, histiocytes and giant cells, but no neoplastic osteoid formation. Treatment is wide surgical excision.

Malignant Vascular Tumors

Hemangioendothelioma. Hemangioendothelioma is a malignant neoplasm arising from vascular endothelium in long bones. Radiographs show a metadiaphyseal lytic lesion with a “soap bubble” appearance. Histology reveals eosinophilic cells in a basophilic stroma. Lesions may be multifocal. Treatment consists of curettage for low-grade lesions and wide excision for high-grade lesions.

Hemangiopericytoma

Hemangiopericytoma is usually a solitary lesion occurring in the soft tissues or the axial skeleton and proximal long bones in middle-aged or elderly males. Histology reveals branching “staghorn” vascular spaces. The tumor cells resemble cells normally seen adjacent to capillaries. Treatment is wide excision.

Angiosarcoma of Bone

Angiosarcoma is a soft tissue malignancy usually seen in elderly males. Histology reveals vascular channels with anaplasia. Treatment is wide excision, or if inaccessible surgically, radiation.

MISCELLANEOUS TUMORS

Giant Cell Tumor of Bone

Giant cell tumor occurs in the knee, distal radius, proximal humerus, and pelvis in women 20 to 40 years of age. Presenting complaints include pain and pathologic fracture. Imaging reveals eccentric, epimetaphyseal lytic lesions eroding the subchondral bone. Histology reveals multinucleate giant cells and mononuclear stromal cells (Fig. 43-23). These tumors can occasionally metastasize to the chest. Primary malignant giant cell tumor has a poor prognosis. Treatment of giant cell tumors is with curettage and high-speed burr. Recurrence rates are high with simple curettage, and the use of cryosurgery, phenol, or polymethylmethacrylate bone cement may help decrease recurrence rates. After pathologic fractures, wide excision may

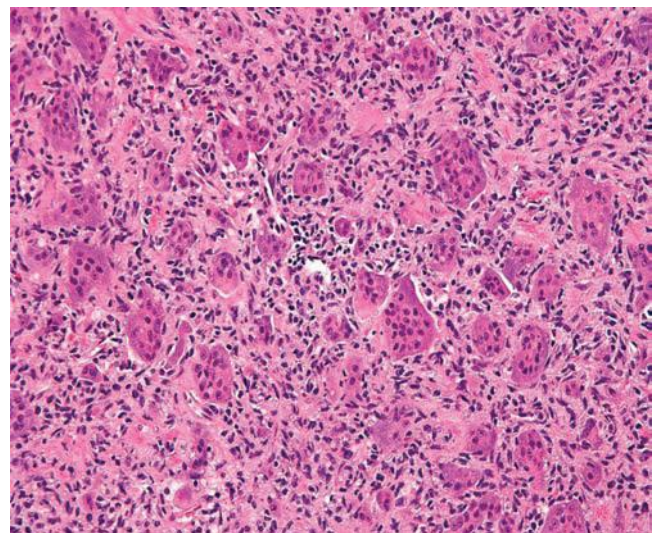


Figure 43-23. Giant cell tumor.

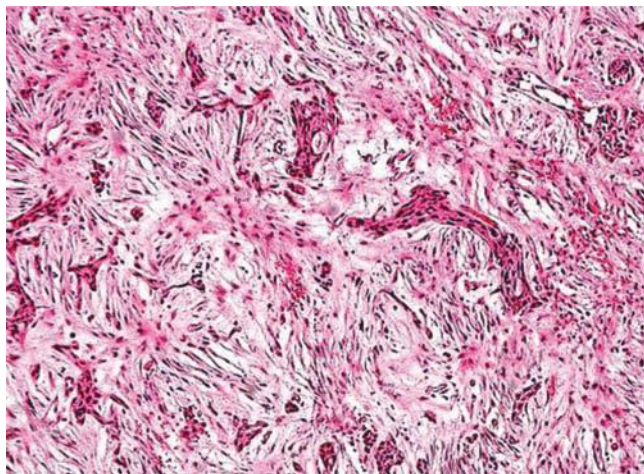


Figure 43-24. Adamantinoma.

be required. In tumors that are inaccessible surgically, radiation may be indicated.

Ossifying Fibroma and Adamantinoma

Ossifying fibroma occurs in the anterior cortex of the tibial diaphysis of young males. Radiographs have a soap bubble appearance. Patients may present with pain but often the diagnosis is incidental on radiographs. Histology resembles fibrous dysplasia, but with osteoblastic rimming. Ossifying fibroma may be a precursor to adamantinoma.

Adamantinomas are low grade malignancies capable of metastasis seen in the tibia. Histology reveals a tubular, basoid, squamoid, or spindled pattern (Fig. 43-24). While ossifying fibroma is benign, careful monitoring is needed because they may be a precursor of adamantinoma. The treatment of adamantinoma is with wide surgical excision.

Primary Lymphoma of Bone

Primary lymphoma accounts for about 5% of all neoplasms of bone. Long bone involvement is more frequent than spine. Lymphoma of bone typically occurs in males in their forties. Histology reveals large B cell lymphomas. Treatment is a combination of chemotherapy and radiation. Surgery may be required for stabilization of pathologic fractures.

Chordoma

Chordoma arises from notochordal rests in the sacrum. These tumors are found in middle-aged to older men and presents with bladder and bowel symptoms. An MRI shows a destructive lesion with a large soft-tissue mass. Histology shows epithelioid cells arranged in cords with vacuolated physaliferous cells. Treatment is surgical excision and muscle flaps and a mesh for reconstruction. Urinary diversion and colostomy may be needed for loss of bladder and bowel control.

Multiple Myeloma

Myeloma, the most common primary bone malignancy, is a proliferative disorder of B cells, with plasma cells, evidence of monoclonal M protein in the serum and/or urine, and hypercalcemia, renal insufficiency, anemia, or bone disease. A solitary myeloma lesion in bone is known as a *plasmacytoma* (Fig. 43-25). Presenting symptoms in myeloma range from bone pain and osteopenia, to focal lytic lesions with pathologic fractures and hypercalcemia. Myeloma protein 1-alpha stimulates

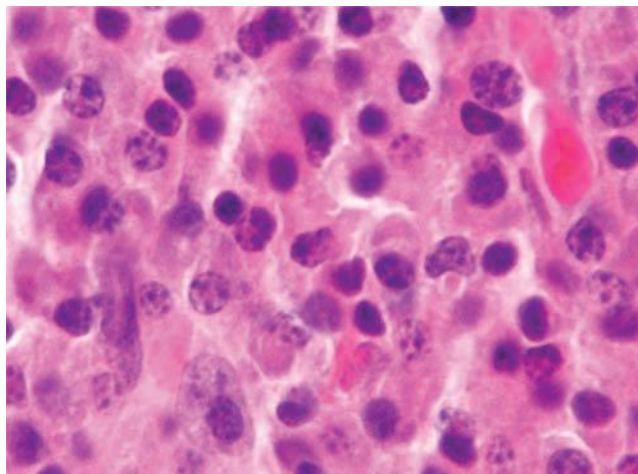


Figure 43-25. Plasmacytoma.

osteoclast formation. Osteoclast activating factors increase receptor activator of nuclear factor κ B ligand (RANKL) in the bone marrow. RANKL induces osteoclast differentiation and activation. Myeloma cells inhibit osteoblast differentiation and activity. Serum and urine electrophoresis detect the M protein. Work up also includes complete blood cell count, erythrocyte sedimentation rate, calcium levels, renal function assessment, and β -2-microglobulin levels, and a skeletal survey. Bone scans may show a false-negative result in more than two-thirds of patients and a dual energy X-ray absorptiometry scan. Plasmacytoma is usually treated with radiation to the lesion. Myeloma is treated with chemotherapy, stem cell transplantation, and radiation therapy. Many patients with myeloma develop a vertebral compression fracture. Kyphoplasty can be useful in providing pain relief. The risks of cement extravasation and related complications are lower with kyphoplasty than with vertebroplasty. If there is instability or if there is neural compression, surgical stabilization may be required.

METASTATIC BONE TUMORS

Metastatic bone tumors are more common than primary bone tumors. Metastatic tumors affect the lung, liver, and bone. Cancers that commonly metastasize to bone are breast, prostate, lung, thyroid, and kidney. In patients older than 40 years of age, metastases and myeloma are the most common lesions in bone. The most common site of involvement is the axial skeleton and proximal ends of long bones. Bronchogenic and renal cell carcinomas can metastasize distal to the knee and elbow. Malignant cells are able to detach from one location and set up a focus at a distant site. Work up of a patient with suspected metastatic disease to bone should include CT of chest, abdomen, and pelvis, mammography, tumor markers, serum, and urine electrophoresis, and bone scans.

PEDIATRIC ORTHOPEDICS

BIRTH INJURIES

Brachial Plexus Palsy

Injury of the brachial plexus during delivery occurs in two births in every 1000. Large birth weight, forceps delivery, breech presentation, and prolonged labor are risk factors. Brachial plexus

injury usually represents a stretch injury on the nerve roots. Management is therapy and passive exercise to preserve motion in the shoulder while awaiting return of neurologic and motor function. Surgical repair of injured nerve roots and trunks may be required in severe cases.

Cerebral Palsy

Cerebral palsy results from an injury to the brain which may be associated with mental impairment. Cerebral palsy is classified as spastic, athetotic, ataxic, and may present with spasticity, hemiplegia, diplegia, or scoliosis. The typical cerebral palsy patient is hyperreflexic with increased muscle tone and spasm. Treatment includes tendon lengthening procedures, release of contractures, and tendon transfers to maintain motion and function.

Hip dislocation or subluxation results from unbalanced muscle forces in many cerebral palsy patients. Treatment consists of abductor tendon releases. When soft tissue releases are unsuccessful, tendon balancing procedures may be combined with open reduction of a hip joint and acetabular reconstruction and osteotomy of the proximal femur. Knee contractures are treated with hamstring lengthening.

Foot and ankle deformities are treated even in nonambulatory patients to facilitate shoe wear. The most common foot deformity in cerebral palsy is an equinovalgus foot caused by heel cord contracture and peroneal spasm. Tendon balancing is usually necessary and bony reconstruction may also be needed in severe cases.

Skeletal Growth

Injury, inflammatory disease, and developmental disorders in actively growing bones requires special attention to preserving the growth plates. The pediatric skeleton is incompletely ossified making diagnosis of an injury difficult, since significant portions of the skeleton are invisible on radiographs. The epiphysis, generally containing an articular surface, is found at the ends of the long bone. The physis or growth plate is found beneath the epiphysis. The physis has six specific zones: the *reserve zone*, the *zone of differentiation*, the *zone of proliferation*, the *zone of maturation*, the *hypertrophic zone*, and finally, the *zone of calcification*.

Injury or insult to the growth plate can lead to premature growth arrest or angular deformity of the limb. Surrounding the metaphyseal and diaphyseal bone, is the periosteum. This metabolically active layer of tissue synthesizes new bone onto the diaphyseal and metaphyseal bone and provides circumferential growth of the bones.

Ossification centers in the epiphysis and appear in a predictable order, and can help determine “bone age.”

Pediatric Fractures

In a pediatric patient, the epiphyseal growth plate is unossified and at risk of fracture. Reduction and stabilization of epiphyseal fractures is critical to minimize permanent growth disturbances and deformity.

Classification of Growth Plate Injuries

Salter and Harris described a useful classification for epiphyseal fractures. A Salter-Harris Type I injury is a simple transverse fracture through the physis. A Salter-Harris Type II fracture contains a component of fracture through the growth plate in continuity with a fracture of the metaphysis. Salter-Harris Type III fracture occurs through the physis and exits through the growth plate. While a Salter-Harris Type IV fracture line extends

through the physis from the metaphysis into the epiphysis. A Salter-Harris Type V fracture crushes the physis itself.

Treatment of growth plate fracture requires anatomic reduction of the fragments. Internal fixation avoids placing hardware across the growth plate to minimize the chance of premature growth plate closure.

Diaphyseal Injuries in a Pediatric Patient

Long bones diaphyseal fractures are generally treated closed. Pediatric patients are capable of extensive remodeling so that an angular deformity within the plane of an adjacent joint is often completely remodeled by the growth of the child. When internal fixation of a diaphyseal fracture is required, the physis is avoided.

Fractures of the Pediatric Hip

Pediatric patients with hip fractures may be treated with a spica cast. The spica cast includes the abdomen, lower back, pelvis, and lower limb, and derives its name from the resemblance of the plaster wrap over the hip to wheat (“spica”).

Fractures of the Femoral Shaft

Femoral shaft fractures in a child younger than six years old may be managed with a spica cast. Femur fractures in patients older than six years of age can be managed by internal fixation with a flexible intramedullary nail. Children 14 years of age are treated with an adult style intramedullary reamed nail. Extra-articular fractures of the distal femur or proximal tibia are managed in a long leg cast.

Pediatric Ankle Fractures

Salter-Harris I and II fractures are managed with casting. Salter-Harris III or IV fractures are managed by closed reduction and internal fixation with percutaneous pins or screws. Smooth pins are used, and the physis is avoided unless necessary for stability.

The Tillaux (Salter-Harris Type II) fracture involves a fracture through the lateral epiphysis and the lateral physis. In these patients the growth plate is in the process of closing and open reduction and internal fixation is needed. The “triplane” fracture (Salter-Harris Type IV) is managed by closed reduction with percutaneous pinning.

Pediatric Elbow Fractures

Management of pediatric elbow fractures is complex. A fracture of the distal humeral epiphysis can be misdiagnosed as a dislocation of the elbow. Familiarity with the timing of the ossification centers’ appearance aids in diagnosis. Treatment is closed reduction and percutaneous pinning.

Injury to the brachial artery, the radial, ulnar, and medial nerves are possible. Neurovascular exam is required before, during, and after treatment. Close follow-up for maintenance of reduction and neurovascular status is needed.

DEVELOPMENTAL DISEASE

Developmental Dysplasia of the Hip

Developmental dysplasia of the hip (DDH) is seen in firstborn females with a positive family history, and breech birth.

Untreated hip dislocations can lead to a dysplastic acetabulum. Newborns are examined for hip instability within the first 72 hours. Ortolani’s test consists of gentle elevation and abduction of the femur causing a palpable click in the relocation of a dislocated hip. Barlow’s test is gentle adduction and depression of the femur which causes a palpable click as a hip slips into a dislocated position. Infants with a dislocated or dislocatable hip

will have apparent length discrepancies of the femur when hip is positioned in 90 degrees. Since the bones are not yet ossified, X-ray images of the acetabulum and femoral head are not reliable for diagnosis. Ultrasound can often demonstrate a dislocated or dislocatable hip. Early treatment with abduction and flexion in a Pavlik harness can result in a normal hip joint.

Treatment of DDH

In a child with a dislocatable hip, a Pavlik harness can maintain the hips in flexion and abduction. Avoid severe abduction to avoid avascular necrosis of the head. For mild to moderate dysplasia, 6 to 12 weeks in a Pavlik harness is sufficient. In severe disease, adductor tenotomy may be needed.

If treatment is delayed, open reduction may be necessary. Through an anterior approach the pulvinar can be removed and the femoral head located. Adductor tenotomy and femoral shortening may be indicated. Osteonecrosis of the femoral head can result from open reduction resulting in pain and decreased motion. Some patients with severe DDH may require pelvic osteotomy creating an acetabular shelf, or a varus osteotomy of the proximal femur, or a combination of the two.

Legg-Calvé-Perthes Disease

Osteonecrosis of the proximal femoral epiphysis can cause flattening of the femoral head called Legg-Calvé Perthes disease. The typical patient is a 7-year-old male who presents with groin or knee pain, decreased hip motion, and a limp. Treatment includes traction, physical therapy, abduction exercises, and crutches. Femoral and pelvic osteotomies may be needed in extreme cases.

Slipped Capital Femoral Epiphysis

Children ages 10 to 16 years old can develop displacement of the epiphysis on the femoral neck with no history of injury. Slipped capital femoral epiphysis (SCFE) is associated with African American heritage, obesity, and is more common in boys than in girls. One-quarter of cases are bilateral. Patients generally present with groin and anterior thigh or even knee pain and decreased motion. In pediatric patients with knee pain, assess the ipsilateral hip as well.

Treatment for slipped capital femoral epiphysis patients is percutaneous screw fixation through the femoral neck to engage the epiphysis. Reduction of the slipped epiphysis is not recommended because of an increased risk of avascular necrosis. One screw is adequate to prevent further slip.

Lower Extremity Rotational Abnormalities

Intoeing can result from femoral anteversion, tibial torsion, and metatarsus adductus. Remember that a mild degree of intoeing is normal in young children 3 to 5 years of age.

Excessive internal rotation of the femur will usually correct by age 8. Severe rotation with functional impairment that does not correct by age 10 or 11 may require rotational femoral osteotomy.

Bilateral intoeing gait in one- and two-year-old children can result from tibial torsion which generally will completely resolve without treatment.

Metatarsus adductus in infants will also resolve spontaneously in most cases.

Congenital Talipes Equinovarus

Club foot is a common problem associated with contractures of the medial tendons of the foot, a tight Achilles tendon, and contractures of the ankle, hindfoot, and midfoot. Talipes equinovarus can be corrected by sequential corrective casting

of the foot. A successful program of casting may be complete in one to five months. In patients with severe disease or who initiate treatment after nine months of age, surgical release of contracted soft tissues may be necessary.

Osgood-Schlatter Disease

Osgood-Schlatter disease is a common problem most often seen in athletically active adolescents. This disorder is characterized by ossification in the distal patellar tendon at the point of its tibial insertion. This disorder is thought to result from mechanical stress on the tendinous insertion. Radiographs show calcified ossicles within the tendon at its insertion. The disease presents with severe local pain and tenderness in the area of the tibial tubercle.

Treatment for the disease is activity restriction. If the symptoms are improved, athletic participation can be resumed. Symptoms regress after skeletal maturity or the discontinuance of active athletic participation.

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44

chapter

Surgery of the Hand and Wrist

Scott D. Lifchez and J. Alex Kelamis

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INTRODUCTION

The highly mobile, functional, and strong hand is a major distinguishing point between humans and the nonhuman primates. The hand is an essential participant for activities of daily living, vocation, and recreational activities. The hand is even adaptable enough to read for the blind and speak for the mute. The underlying goal of all aspects of hand surgery is to maximize mobility, sensibility, stability, and strength while minimizing pain. These goals are then maximized to the extent possible given the patient's particular pathology. Hand surgery is a regional specialty. Hand surgeons integrate components of neurologic, orthopedic, plastic, and vascular surgery in the care of patients with disorders of the upper extremities.

ANATOMY OF THE HAND AND WRIST

In order to understand any disorder of the hand, one must understand the anatomy of the underlying structures. Examination of the hand is based on demonstrating the function or lack thereof of each of these structures.

Bones

The hand is highly mobile in space to allow maximum flexibility in function. As such, a number of directions particular to the hand are necessary in order to properly describe position, motion, and so on.¹ Palmar (or volar) refers to the anterior surface of the hand in the anatomic position; dorsal refers to the posterior surface in the anatomic position. The hand can

Key Points

- 1▶ Surgery of the hand is a regional specialty, integrating components of neurologic, orthopedic, plastic, and vascular surgery.
- 2▶ Understanding hand anatomy is the key to proper diagnosis of injury, infection, and degenerative disease of the hand.
- 3▶ After evaluation and/or treatment, patients should be splinted to protect the injured digits and keep the collateral ligaments of the injured joints on tension (metacarpophalangeal joints flexed, interphalangeal joints extended).
- 4▶ Healing of an injured or diseased structure in the hand is not the endpoint of treatment; the goal of any intervention must be

to obtain structure healing, relief of pain, and maximization of function.

- 5▶ If a patient managed conservatively for cellulitis does not improve within 24 to 48 hours of appropriate intravenous antibiotics, abscess must be suspected.
- 6▶ Clinical examination, particularly noting the area of greatest tenderness and/or inflammation, is the most useful diagnostic tool for hand infections.

rotate at the wrist level; rotation to bring the palm down is called pronation, rotation to bring the palm up is called supination. Because the hand can rotate in space, the terms medial and lateral are avoided. Radial and ulnar are used instead as these terms do not vary with respect to the rotational position of the hand. Abduction and adduction, when used on the hand, refer to movement of the digits away from and toward the middle finger, respectively (Fig. 44-1).

The hand is comprised of 19 bones arranged in five rays.² A *ray* is defined as a digit (finger or thumb) from the metacarpal base to the tip of the digit (Fig. 44-2A). The rays are numbered 1 to 5, beginning with the thumb. By convention, however, they are referred to by name: thumb, index, middle, ring, and small. There are five metacarpals, comprising the visible palm of the hand. Each digit has a proximal and a distal phalanx, but only the fingers have a middle phalanx as well. The metacarpophalangeal (MP) joint typically allows 90° of flexion with a small amount of hyperextension. In addition, the fingers can actively abduct (move away from the middle finger) and adduct (move toward the middle finger). The thumb, in contrast, moves principally in the flexion-extension arc at the MP joint. Although there can be laxity in the radial and ulnar direction, the thumb cannot actively move in these directions at the MP level. The proximal interphalangeal joint (PIP) is the critical joint for finger mobility. Normal motion is 0 to 95° (full extension to flexion). The distal interphalangeal joint (DIP) also moves only in a flexion-extension plane from 0 to 90° on average. The thumb interphalangeal joint (IP) also moves only in a flexion-extension plane. Its normal motion is highly variable between individuals, but averages 0 to 80°.

Each of the MP and IP joints has a radial and ulnar collateral ligament to support it. The IP joint collateral ligaments are on tension with the joint fully extended. For the fingers, the MP joint collateral ligaments are on tension with the joint bent 90°. Collateral ligaments have a tendency to contract when not placed on tension; this becomes relevant when splinting the hand (see later Trauma section on splinting).

The wrist consists of eight carpal bones divided into two rows (Fig. 44-2B).² The proximal row consists of the scaphoid, lunate, and triquetrum. The lunate is the principle axis of motion of the hand onto the forearm. It bears approximately 35% of the load of the wrist onto the forearm. The scaphoid is shaped like the keel of a boat and bears 55% of the load of the hand onto the forearm, but also serves as the principle link between the proximal and distal rows, allowing for motion while

maintaining stability. Both the scaphoid and the lunate articulate with the radius. The triquetrum resides ulnar to the lunate. It does not interact with the ulna proximally; rather, it interacts with a cartilage suspended between the ulnar styloid and the distal radius called with triangular fibrocartilage complex (TFCC) (Fig. 44-2B). The remaining 10% of load of the hand onto the forearm is transmitted through the TFCC.³

The distal row consists of four bones. The trapezium resides between the scaphoid and the thumb metacarpal. Distally, it has a saddle-shaped surface, which interacts with a reciprocally saddle-shaped base of the thumb metacarpal to allow for high mobility of the thumb carpometacarpal (CMC) joint in radial-ulnar and palmar-dorsal directions and opposition (Fig. 44-1B). The trapezoid rests between the scaphoid and the index finger metacarpal. The capitate, the largest carpal bone and first to ossify in a child, lies between the lunate and the middle finger metacarpal, but also interacts with the scaphoid on its proximal radial surface. The index and middle finger CMC joints are highly stable and have minimal mobility. The hamate is the ulnar-most bone in the distal row, sitting between the triquetrum proximally and the ring and small finger metacarpals distally. The ring and small finger CMC joints are mobile, principally in the flexion-extension direction.

The pisiform is a carpal bone only by geography. It is a sesamoid bone within the FCU tendon (see below). It does not bear load and can be excised, when necessary, without consequence.

Muscles Affecting the Hand and Wrist

The wrist is moved by multiple tendons that originate from the forearm and elbow. The digits of the hand are moved by both intrinsic (originating within the hand) and extrinsic (originating in the forearm) muscles. All of these muscles are innervated by the median, radial, or ulnar nerves (or their branches) (Fig. 44-3).

Three muscles flex the wrist, all of which originate from the medial epicondyle of the humerus. The flexor carpi radialis (FCR, median nerve) inserts on the volar base of the index finger metacarpal. The flexor carpi ulnaris (FCU, ulnar nerve) also originates from the proximal ulna and inserts on the volar base of the small finger metacarpal. The palmaris longus (PL) tendon does not insert on a bone; it inserts on the palmar fascia, located deep to the skin in the central proximal palm, and is absent in up to 15% of patients. The FCR also deviates the wrist radially, whereas the FCU deviates the wrist ulnarly.

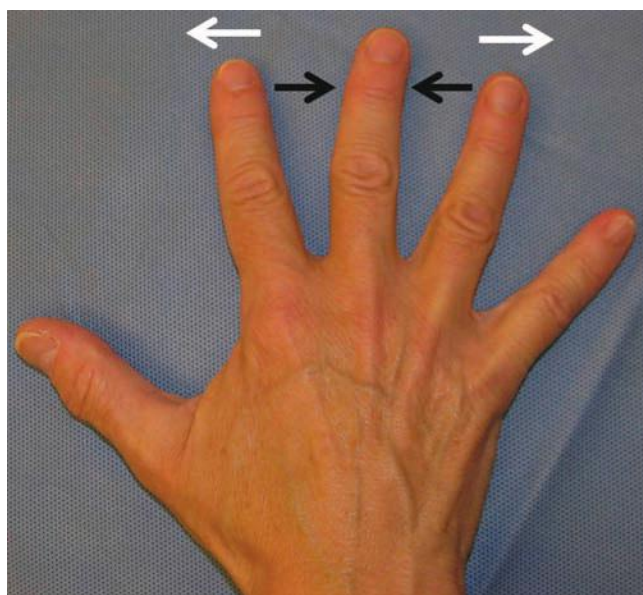
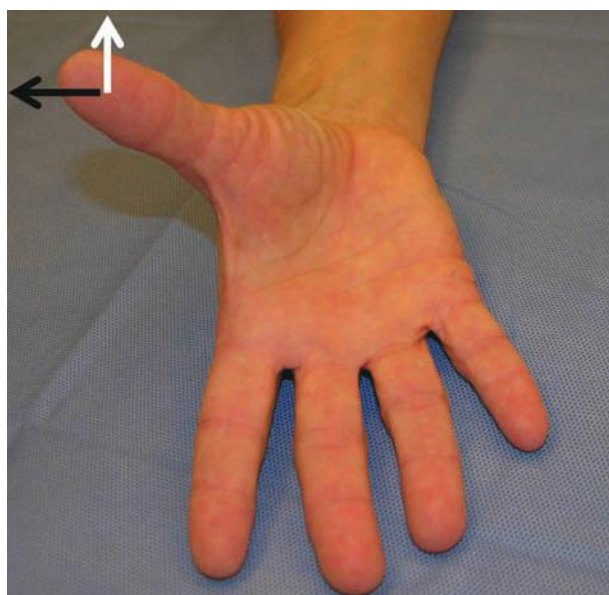
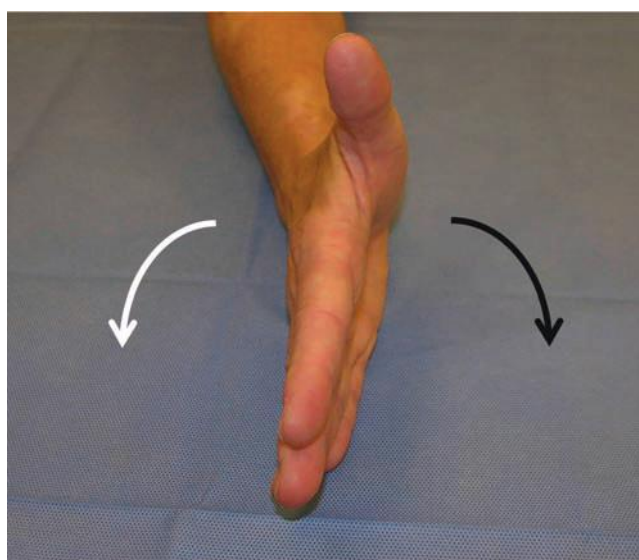
**A****B****C****D**

Figure 44-1. Directions of finger, hand, and wrist motion. **A.** Finger abduction (*white arrows*) and adduction (*black arrows*). **B.** Thumb radial (*black arrow*) and palmar (*white arrow*) abduction. **C.** Thumb and small finger opposition. **D.** Hand/wrist pronation (*black arrow*) and supination (*white arrow*).

All three wrist extensors are innervated by the radial nerve or its branches. The extensor carpi radialis longus (ECRL) originates from the distal shaft of the humerus and inserts on the dorsal base of the index finger metacarpal. The extensor carpi radialis brevis (ECRB) originates from the lateral epicondyle of the humerus and inserts on the dorsal base of the middle finger metacarpal. The extensor carpi ulnaris (ECU) also originates from the lateral epicondyle of the humerus and inserts on the dorsal base of the small finger metacarpal. The ECRL deviates the wrist radially, whereas the ECU deviates the wrist ulnarly.

The long flexors of the fingers all originate from the medial epicondyle of the humerus. The flexor digitorum superficialis (FDS) inserts on the base of the middle phalanx of each finger and primarily flexes the PIP joint. The flexor digitorum profundus (FDP) inserts on the base of the distal phalanx and

primarily flexes the DIP joint. The flexor pollicis longus (FPL) originates more distally, from the ulna, radius, and interosseous membrane between them in the forearm. It inserts on the base of the distal phalanx of the thumb and primarily flexes the IP joint. All of these tendons can also flex the more proximal joint(s) in their respective rays. All of these muscles are innervated by the median nerve (or its branches) except the FDP to the ring and small fingers, which are innervated by the ulnar nerve.

The extrinsic extensors of the fingers and thumb are all innervated by the posterior interosseous nerve (PIN, branch of the radial nerve). The extensor digitorum communis (EDC) originates from the lateral epicondyle of the humerus and extends the MP joints of the fingers. Unlike most tendons that attach directly into a bone, the EDC tendons do not insert on the dorsal base of the proximal phalanx, but rather into a soft tissue sling called the



Figure 44-2. Bony architecture of the hand and wrist. **A.** Bones of the hand and digits. All rays have metacarpophalangeal (MP) joints. The fingers have proximal and distal interphalangeal (PIP and DIP), but the thumb has a single interphalangeal (IP) joint. **B.** Bones of the wrist. The proximal row consists of the scaphoid, lunate, and capitate. The distal row bones articulate with the metacarpals: the trapezium with the thumb, the trapezoid with the index, the capitate with the middle, and the hamate with the ring and small. The pisiform bone is a sesamoid within the flexor carpi ulnaris tendon. It overlaps the triquetrum and hamate but does not contribute to a carpal row. CMC = carpometacarpal; TFCC = triangular fibrocartilage complex.

sagittal hood, which surrounds the proximal phalanx base and pulls up on the volar surface in a hammock-like manner. More distally in the dorsal forearm, the extensor indices proprius (EIP) and extensor digiti quinti (EDQ) originate from the ulna, radius, and posterior interosseous membrane and insert on the sagittal hood of the index and small fingers, respectively.

The thumb has three separate extrinsic extensors. All of these originate from the dorsal ulna in the mid-forearm and are innervated by the PIN. The abductor pollicis longus (APL) inserts on the radial base of the thumb metacarpal to produce some extension, but mostly abduction. The extensor pollicis brevis (EPB) inserts on the base of the thumb proximal phalanx.

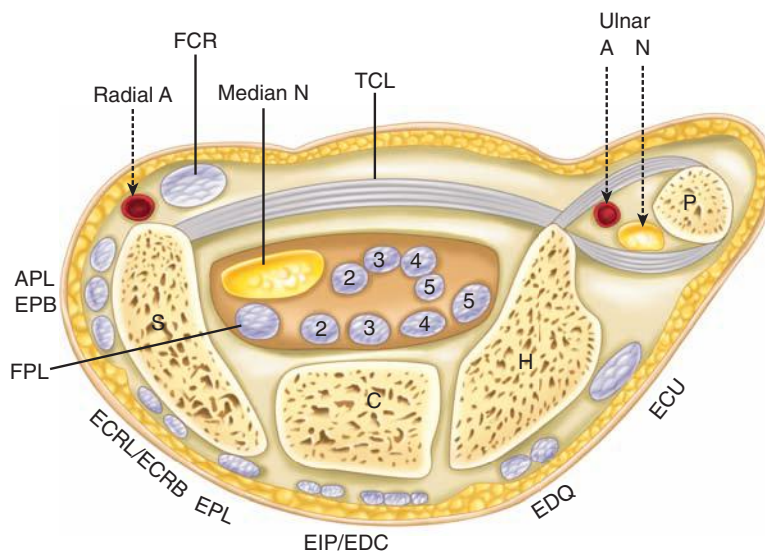


Figure 44-3. Cross-section of the wrist at the midcarpal level. The relative geography of the neurologic and tendinous structures can be seen. The transverse carpal ligament (TCL) is the roof of the carpal tunnel, passing volar to the median nerve and long flexor tendons. The TCL is also the floor of the ulnar tunnel, or Guyon's canal, passing dorsal to the ulnar artery and nerve. The wrist and digital extensor tendons are also seen, distal to their compartments on the distal radius and ulna. Bones: C = capitate; H = hamate; P = pisiform; S = scaphoid. Tendons (flexor digitorum superficialis is volar to flexor digitorum profundus within the carpal tunnel): 2 = index finger; 3 = middle finger; 4 = ring finger; 5 = small finger. A = artery; APL = abductor pollicis longus; ECRB = extensor carpi radialis brevis; ECRL = extensor carpi radialis longus; ECU = extensor carpi ulnaris; EDC = extensor digitorum communis; EDQ = extensor digiti quinti; EIP = extensor indices proprius; EPB = extensor pollicis brevis; EPL = extensor pollicis longus; FCR = flexor carpi radialis; FPL = flexor pollicis longus; N = nerve.

The extensor pollicis longus (EPL) inserts on the base of the thumb distal phalanx.

The intrinsic muscles of the hand are what allow humans fine, subtle movements of the hand. Microsurgery, typing, and even video gaming would be difficult, if not impossible, without them.

The thenar muscles originate from the volar radial surface of the scaphoid and trapezium and the flexor retinaculum. The abductor pollicis brevis (APB) inserts on the radial base of the thumb proximal phalanx and abducts the thumb in a radial and volar direction. The opponens pollicis (OP) inserts on the radial distal aspect of the thumb metacarpal and draws the thumb across the palm toward the small finger. The flexor pollicis brevis (FPB) inserts on the base of the thumb proximal phalanx and flexes the thumb MP joint. The APB, OP, and superficial head of the FPB are all innervated by the thenar motor branch of the median nerve.

The lumbrical muscles are unique in the body in that they originate from a tendon. Each finger's lumbrical originates from the FDP tendon in the palm. The lumbrical tendon passes along the radial aspect of the digit to flex the MP and extend the IP joints. The index and middle lumbricals are median nerve innervated, and the ring and small finger lumbricals are ulnar nerve innervated.

The hypothenar muscles originate from the pisiform, hamate, and flexor retinaculum and insert on the ulnar base of the small finger proximal phalanx. The abductor digiti quinti (ADQ) abducts the small finger. The opponens digiti quinti (ODQ) brings the small finger across the palm in reciprocal motion to the OP. The flexor digiti quinti (FDQ) flexes the small finger metacarpal. All of these muscles are innervated by the ulnar nerve.

The interosseous muscles occupy the space between the metacarpal bones. Their tendons insert on the bases of the proximal phalanges. All act to flex the MP joints and extend the IP joints. The three palmar interosseous muscles adduct the fingers. The four dorsal interosseous muscles abduct the fingers. The adductor pollicis originates from the middle finger metacarpal and inserts on the ulnar base of the thumb proximal phalanx. It acts to adduct the thumb. All of these muscles, as well as the deep head of the FPB, are innervated by the ulnar nerve.

Tendons and Pulleys

Multiple pulleys pass over or surround the extrinsic tendons en route to or within the hand. Their purpose is to maintain tendon position near the bone, allowing maximal translation of tendon excursion into joint motion.

The most well known of the wrist-level pulleys is the flexor retinaculum, also known as the transverse carpal ligament. It attaches to the scaphoid tubercle and trapezium radially and the hook of the hamate bone and pisiform ulnarly. Deep to this ligament, between the scaphoid (radially) and the hamate (ulnarly), pass the FDS, FDP, and FPL tendons as well as the median nerve. This area is also known as the carpal tunnel (see Fig. 44-3).

On the dorsum of the wrist, the extensor retinaculum is divided into six compartments. Beginning on the radial aspect of the radius, the first compartment contains the APL and EPB tendons. The second holds the ECRL and ECRB tendons. The EPL passes through the third compartment. The fourth compartment contains the EIP and EDC tendons, the fifth the EDQ, and the sixth the ECU. The sixth compartment is located on the

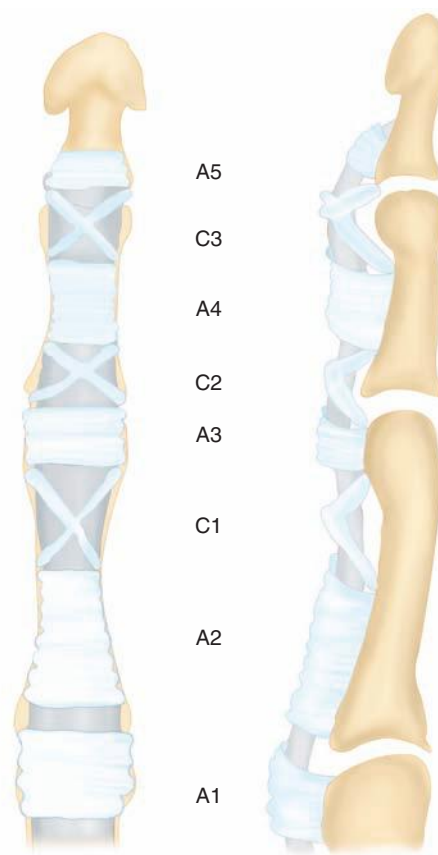


Figure 44-4. Drawing of anteroposterior and lateral view of the pulley system.

ulnar aspect of the distal ulna. Although the compartments end at the radiocarpal/ulnocarpal joints, the relative geography of the tendons is preserved over the carpal bones (see Fig. 44-3).

In the hand, the pulleys maintain the long flexor tendons in close apposition to the fingers and thumb. There are no extensor pulleys within the hand. Each finger has five annular and three cruciate pulleys (Fig. 44-4). The second and fourth (A2 and A4) pulleys are the critical structures to prevent bowstringing of the finger.⁴ The remaining pulleys can be divided as needed for surgical exposure or to relieve a stricture area.

Vascular

Two major arteries serve the hand. The radial artery travels under the brachioradialis muscle in the forearm. At the junction of the middle and distal thirds of the forearm, the artery becomes superficial and palpable, passing just radial to the FCR tendon. At the wrist level, the artery splits into two branches. The smaller, superficial branch passes volarly into the palm to contribute to the superficial palmar arch. The larger branch passes dorsally over the scaphoid bone, under the EPL and EPB tendons (known as the anatomic snuffbox) and back volarly between the proximal thumb and index finger metacarpals to form the superficial palmar arch.

The ulnar artery travels deep to the FCU muscle in the forearm. When the FCU becomes tendinous, the ulnar artery resides deep and slightly radial to it. At the wrist, the artery travels between the hamate and pisiform bones superficial to the transverse carpal ligament (known as Guyon's canal) into the palm. The larger, superficial branch forms the superficial palmar arch. The deeper branch contributes to the deep palmar

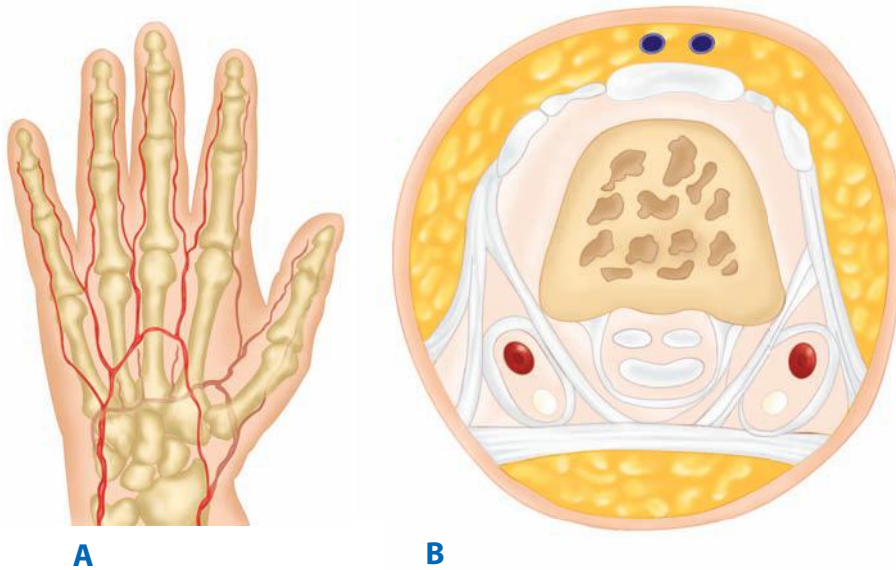


Figure 44-5. Arteries of the hand and finger. **A.** Relative position of the superficial and deep palmar arches to the bony structures and each other; note the radial artery passes dorsal to the thumb metacarpal base, through the first web space, and anterior to the index metacarpal base as it forms the deep arch. **B.** The neurovascular bundles lay volar to the midaxis of the digit with the artery dorsal to the nerve; Grayson's ligament (volar) and Cleland's ligament (dorsal) connect the bone to the skin surrounding the bundle.

arch (Fig. 44-5A). In 97% of patients, at least one of the deep or superficial palmar arches is intact, allowing for the entire hand to survive on the radial or ulnar artery.⁵

Each digit receives a radial and ulnar digital artery. For the thumb, the radial digital artery may come from the deep palmar arch or the main body of the radial artery. The larger ulnar digital artery comes off the deep arch as either a discrete unit, the princeps pollicis artery, or less frequently as the first common digital artery, which then splits into the radial digital artery to the index finger and the ulnar digital artery to the thumb. The second, third, and fourth digital arteries typically branch off the superficial palmar arch and pass over the similarly named interosseous spaces respectively, ultimately dividing into two proper digital arteries each. The ulnar digital artery of the small finger comes off as a separate branch from the superficial arch. Within the finger, the proper digital arteries travel lateral to the bones and tendons, just palmar to the midaxis of the digit, but dorsal to the proper digital nerves (Fig. 44-5B).

Nerve

Three principal nerves serve the forearm, wrist, and hand: the median, radial, and ulnar nerves. The most critical of these from a sensory standpoint is the median nerve. The median nerve begins as a terminal branch of the medial and lateral cords of the brachial plexus. It receives fibers from C5–T1. The palmar cutaneous branch of the median nerve separates from the main body of the nerve 6 cm proximal to the volar wrist crease and serves the proximal, radial-sided palm. The main body of the median nerve splits into several branches after the carpal tunnel: a radial digital branch to the thumb, an ulnar digital nerve to the thumb, and a radial digital nerve to the index finger (sometimes beginning as a single first common digital nerve); the second common digital nerve that branches into the ulnar digital nerve to the index finger and the radial digital nerve to the middle finger; and a third common digital nerve that branches into the ulnar digital nerve to the middle finger and a radial digital nerve to the ring finger. The digital nerves provide volar-sided sensation from the metacarpal head level to the tip of the digit. They also, through their dorsal branches, provide dorsal-sided sensation to

the digits from the midportion of the middle phalanx distally via dorsal branches. The thenar motor branch of the median nerve most commonly passes through the carpal tunnel and then travels in a recurrent fashion back to the thenar muscles. Less commonly, the nerve passes through or proximal to the transverse carpal ligament en route to its muscles.

In the forearm, the median nerve gives motor branches to all of the flexor muscles except the FCU, and the ring and small finger portions of the FDP. Distal median motor fibers (with the exception of those to the thenar muscles) are carried through a large branch called the anterior interosseous nerve.

The ulnar nerve is a terminal branch of the medial cord of the brachial plexus. It receives innervation from C8 and T1 roots. The FCU and FDP (ring/small) receive motor fibers from the ulnar nerve. In the distal forearm, 5 cm above the head of the ulna, the nerve gives off a dorsal sensory branch. Once in the hand, the nerve splits into the motor branch and sensory branches. The motor branch curves radially at the hook of the hamate bone to innervate the intrinsic muscles, as described earlier. The sensory branches become the ulnar digital nerve to the small finger and the fourth common digital nerve, which splits into the ulnar digital nerve to the ring finger and the radial digital nerve to the small finger. The sensory nerves provide distal dorsal sensation similar to the median nerve branches.

The radial nerve is the larger of two terminal branches of the posterior cord of the brachial plexus. It receives fibers from C5–T1 nerve roots. It innervates all of the extensor muscles of the forearm and wrist through the PIN branch except for the ECRL, which is innervated by the main body of the radial nerve in the distal upper arm. There is no ulnar nerve contribution to extension of the wrist, thumb, or finger MP joints. As noted earlier, the ulnar innervated intrinsic hand muscles are the principle extensors of the finger IP joints, although the long finger extensors (EDC, EIP, EDQ) make a secondary contribution to this function.

In the proximal dorsal forearm, the superficial radial nerve (SRN) is the other terminal branch of the radial nerve. It travels deep to the brachioradialis muscle until 6 cm proximal to the radial styloid, where it becomes superficial. The SRN provides sensation to the dorsal hand and the radial three and a half digits up to the

level of the mid-middle phalanx (where the dorsal branches of the proper digital nerves take over, as described earlier). The dorsal branch of the ulnar nerve provides sensation to the ulnar one and a half digits and dorsal hand in complement to the SRN.

HAND EXAMINATION

Emergency Room/Inpatient Consultation

A common scenario in which the hand surgeon will be introduced to the patient is in trauma or other acute situations. The patient is evaluated by inspection, palpation, and provocative testing.

On inspection, one should first note the position of the hand. The resting hand has a normal cascade of the fingers, with the small finger flexed most and the index finger least (Fig. 44-6). Disturbance of this suggests a tendon or skeletal problem. Also note any gross deformities or wounds and what deeper structures, if any, are visible in such wounds. Observe



Figure 44-6. In the normal resting hand, the fingers assume a slightly flexed posture from the index finger (least) to the small finger (most).

for abnormal coloration of a portion or all of the hand (this can be confounded by ambient temperature or other injuries), edema, and/or clubbing of the fingertips.

Palpation typically begins with the radial and ulnar artery pulses at the wrist level. Pencil Doppler examination can supplement this and evaluate distal vessels. A pulsatile signal is normally detectable by pencil Doppler in the pad of the finger at the center of the whorl of creases. Discrepancies between digits should be noted. If all other tests are inconclusive, pricking the involved digit with a 25-gauge needle should produce bright red capillary bleeding. If an attached digit demonstrates inadequate or absent blood flow (warm ischemia), the urgency of completing the evaluation and initiating treatment markedly increases.

Sensation must be evaluated prior to any administration of local anesthetic. At a minimum, light and sharp touch sensation should be documented for the radial and ulnar aspects of the tip of each digit. Beware of writing “sensation intact” at the conclusion of this evaluation. Rather, one should document what was tested (e.g., “light and sharp touch sensation present and symmetric to the tips of all digits of the injured hand”). In the setting of a sharp injury, sensory deficit implies a lacerated structure until proven otherwise. Once sensation has been evaluated and documented, the injured hand can be anesthetized for patient comfort during the remainder of the examination (see below).

Ability to flex and extend the wrist and digital joints is typically examined next. At the wrist level, the FCR and FCU tendons should be palpable during flexion. The wrist extensors are not as readily palpated due to the extensor retinaculum. Ability to flex the DIP joint (FDP) is tested by blocking the finger at the middle phalanx level. To test the FDS to each finger, hold the remaining three fingers in slight hyperextension and ask the patient to flex the involved digit (Fig. 44-7). This maneuver makes use of the fact that the FDP tendons share a common muscle belly. Placing the remaining fingers in extension prevents the FDP from firing, and allows the FDS, which



Figure 44-7. The examiner holds the untested fingers in full extension, preventing contracture of the flexor digitorum profundus. In this position, the patient is asked to flex the finger, and only the flexor digitorum superficialis will be able to fire.

has a separate muscle belly for each tendon, to fire. Strength in grip, finger abduction, and thumb opposition is tested and compared to the uninjured side. Range of motion for the wrist, MP, and IP joints should be noted and compared to the opposite side.

If there is suspicion for closed space infection, the hand should be evaluated for erythema, swelling, fluctuance, and localized tenderness. The dorsum of the hand does not have fascial septae; thus dorsal infections can spread more widely than palmar ones. The epitrochlear and axillary nodes should be palpated for enlargement and tenderness. Findings for specific infectious processes will be discussed in the Infections section.

Additional exam maneuvers and findings, such as those for office consultations, will be discussed with each disease process covered later in this chapter.

HAND IMAGING

Plain X-Rays

Almost every hand evaluation should include plain X-rays of the injured or affected part. A standard, anteroposterior, lateral, and oblique view of the hand or wrist (as appropriate) is rapid, inexpensive, and usually provides sufficient information about the bony structures to achieve a diagnosis in conjunction with the symptoms and findings.⁶

Lucencies within the bone should be noted. Most commonly, these represent fractures, but they can on occasion represent neoplastic or degenerative processes. Great care should be taken to evaluate the entire X-ray, typically beginning away from the area of the patient's complaint. Additional injuries can be missed, which might affect the treatment plan selected and eventual outcome.

Congruency of adjacent joints should also be noted. The MP and IP joints of the fingers should all be in the same plain on any given view. Incongruity of the joint(s) of one finger implies fracture with rotation. At the wrist level, the proximal and distal edge of the proximal row and proximal edge of the distal row should be smooth arcs,⁷ known as Gilula's arcs (Fig. 44-8A). Disruption of these implies ligamentous injury or possibly dislocation (Fig. 44-8B).



A



B

Figure 44-8. Gilula's arcs are seen shown in this normal patient (**A**) and in a patient with a scaphoid fracture and perilunate dislocation (**B**).

Computed Tomography

Computed tomography (CT) scanning of the hand and wrist can provide additional bony information when plain X-rays are insufficient. Comminuted fractures of the distal radius can be better visualized for number and orientation of fragments. Scaphoid fractures can be evaluated for displacement and comminution preoperatively as well as for the presence of bony bridging postoperatively (Fig. 44-9). CT scans are also useful for CMC fractures of the hand where overlap on a plain X-ray lateral view may make diagnosis difficult.

Unlike the trunk and more proximal extremities, CT scans with contrast are less useful to demonstrate abscess cavities due to the small area of these spaces.

Ultrasonography

Ultrasonography has the advantages of being able to demonstrate soft tissue structures and being available on nights and weekends. Unfortunately, it is also highly operator dependent. In the middle of the night when magnetic resonance imaging (MRI) is not available, ultrasound may be able to demonstrate a large deep infection in the hand but is rarely more useful than a thorough clinical examination.

Magnetic Resonance Imaging

MRI provides the best noninvasive visualization of the soft tissue structures. With contrast, MRI can demonstrate an occult abscess. Unfortunately, it is often not available on an urgent basis for hand issues when this information is often needed. MRI can also demonstrate soft tissue injuries such as cartilage or ligament tears or tendonitis (usually by demonstrating edema in the area in question). It can demonstrate occult fractures that are not sufficiently displaced to be seen on X-ray or CT (again, by demonstrating edema). MRI can also demonstrate vascular disturbance of a bone, as in a patient with avascular necrosis of the scaphoid (Fig. 44-10).

Angiography

Angiography of the upper extremity is rarely used. In many centers, MRI and CT angiography provide sufficient resolution of the vascular structures to make traditional angiography unnecessary.



A



B

Figure 44-9. A. Preoperative images demonstrate a nonunion of a scaphoid fracture sustained 4 years earlier. Postoperatively, cross-sectional imaging with a computed tomography scan in the coronal plan demonstrates bone crossing the previous fracture line. This can be difficult to discern on plain X-rays due to overlap of bone fragments.

Also, primary vascular disease of the upper extremity is relatively uncommon. In the trauma setting, vascular disturbance usually mandates exploration and direct visualization of the structures in question, and angiography is thus obviated.

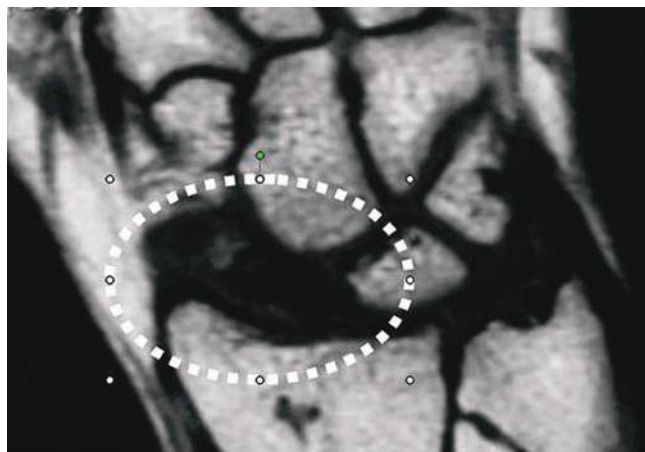


Figure 44-10. T1-weighted magnetic resonance imaging shows perfused bone as white. In this patient, there is the absence of whiteness where the scaphoid should be (*dashed circle*), consistent with avascular necrosis.

For a patient with vascular disease of the upper extremity, angiography of the upper extremity is usually performed through a femoral access much like with the leg. An arterial catheter can be used to deliver thrombolytic drugs to treat a thrombotic process.

TRAUMA

The upper extremity-injured patient may have additional injuries to other parts of the body. All injured patients should receive an appropriate trauma survey to look for additional injuries.

The patient with upper extremity trauma is evaluated as described in the Hand Examination section. Sensory examination should be performed early. Once sensory status has been documented, administration of local anesthesia can provide comfort to the patient during the remainder of the evaluation and subsequent treatment. Patients should receive tetanus toxoid for penetrating injuries if more than 5 years have passed since the last vaccination.

Local Anesthesia

Anesthetic blockade can be administered at the wrist level, digital level, or with local infiltration as needed. Keep in mind that all local anesthetics are less effective in areas of inflammation.

The agents most commonly used are lidocaine and bupivacaine. Lidocaine has the advantage of rapid onset, whereas bupivacaine has the advantage of long duration (average 6–8 hours).⁸ Although bupivacaine can produce irreversible heart block in high doses, this is rarely an issue with the amounts typically used in the hand. For pediatric patients, the tolerated dose is 2.5 mg/kg. This can be easily remembered by noting that when using 0.25% bupivacaine, 1 mL/kg is acceptable dosing.

A commonly held axiom is that epinephrine is unacceptable to be used in the hand. Several recent large series have dispelled this myth.⁹ Epinephrine should not be used in the fingertip and not in concentrations higher than 1:100,000 (i.e., what is present in commercially available local anesthetic with epinephrine). Beyond that, its use is acceptable and may be useful in an emergency room (ER) where tourniquet control may not be available. Also, because most ER procedures are done under pure local anesthesia, many patients will not tolerate the discomfort of the tourniquet beyond 30 minutes.¹⁰ Epinephrine will provide hemostasis and also prolong the effect of the local anesthetic.

Simple lacerations, particularly on the dorsum of the hand, can be anesthetized with local infiltration. This is performed in the standard fashion.

Blocking of the digital nerves at the metacarpal head level is useful for volar injuries distal to this point and for dorsal injuries beyond the midpoint of the middle phalanx (via dorsal branches of the proper digital nerves). Fingertip injuries are particularly well anesthetized by this technique. A digit can be anesthetized via a flexor sheath approach or via the dorsal web space (Fig. 44-11A,B).

Blocking one or more nerves as they cross the wrist can provide several advantages: anesthesia for multiple injured digits, avoiding areas of inflammation where the local anesthetic agent may be less effective, and avoiding injection where the volume of fluid injected may make treatment harder (such as fracture reduction). Four major nerves cross the wrist: the median nerve, SRN, ulnar nerve, and dorsal sensory branch of the ulnar nerve (Fig. 44-11C–E). When blocking the median and ulnar nerves, beware of intraneural injection, which can cause irreversible neural scarring. If the patient complains of severe paresthesias with injection or high resistance is encountered, the needle should be repositioned.

Fractures and Dislocations

For dislocations and displaced fractures, a visible deformity is often present. Nondisplaced fractures may not show a gross deformity but will have edema and tenderness to palpation at the fracture site. A fracture is described by its displacement, rotation, and angulation. A fracture is also described in terms of comminution and the number and complexity of fracture fragments. Displacement is described as a percentage of the diameter of the bone; rotation is described in degrees of supination or pronation with respect to the rest of the hand; angulation is described in degrees. To avoid confusion, it is useful to describe which direction the angle of the fracture points. All injuries should be evaluated for nearby wounds (open) that may introduce bacteria into the fracture site or joint space.

Once the initial force on the fracture ceases, the tendons passing beyond the fracture site provide the principal deforming force. Their force is directed proximally and,

to a lesser extent, volarly. Based on this, the stability of a fracture can be determined by the orientation of the fracture with respect to the shaft of the bone. Transverse fractures are typically stable. Oblique fractures typically shorten. Spiral fractures typically rotate as they shorten and thus require surgical treatment.

Fractures of the tuft of the distal phalanx are common. Catching of a finger in a closing door is a common causative mechanism. These fractures are often nondisplaced and do not require treatment beyond protection of the distal phalanx from additional trauma while the fracture heals.

Displaced transverse fractures of the phalanges can usually be reduced with distraction. The distal part is pulled away from the main body of the hand and then pushed in the direction of the proximal shaft of the finger, and then distraction is released. Postreduction X-rays should routinely be performed to document satisfactory reduction. Oblique and spiral fractures usually are unstable after reduction. The involved digit(s) should be splinted until appropriate surgical intervention can be performed.

Articular fractures of the IP and MP joints are worrisome because they may compromise motion. Chip fractures must be evaluated for instability of the collateral ligaments. If the joint is stable, the patient should initially be splinted for comfort. Motion therapy should be instituted early (ideally within the first week) to prevent stiffness. For larger fractures, the patient should be splinted until surgical treatment can be performed. In surgery, the fracture is typically internally fixated to allow for early motion, again with the goal of preventing stiffness.¹¹

Dislocations of the PIP joints produce traction on the neurovascular structures but usually do not lacerate them. In general, the patient should not be sent home with a joint that remains dislocated. Most commonly, the distal part is dorsal to the proximal shaft and sits in a hyperextended position. For this patient, the examiner gently applies pressure to the base of the distal part until it passes beyond the head of the proximal phalanx. Once there, the relocated PIP joint is gently flexed, confirming the joint is in fact reduced. The joint is splinted in slight flexion to prevent redislocation. On occasion, the head of the proximal phalanx may pass between the two slips of the FDS tendon. For these patients, the joint may not be reducible in a closed fashion.

Angulated fractures of the small finger metacarpal neck (“boxer’s fracture”) are another common injury seen in the ER. Typical history is that the patient struck another individual or rigid object with a hook punch. These are often stable after reduction using the Jahss maneuver (Fig. 44-12).

Fractures of the thumb metacarpal base are often unstable. The Bennett fracture displaces the volar-ulnar base of the bone. The remainder of the articular surface and the shaft typically dislocate dorsoradially and shorten. The thumb often appears grossly shortened, and the proximal shaft of the metacarpal may reside at the level of the trapezium or even the scaphoid on X-ray. In a Rolando fracture, a second fracture line occurs between the remaining articular surface and the shaft. These fractures nearly always require open reduction and internal fixation.

Most nondisplaced fractures do not require surgical treatment. The scaphoid bone of the wrist is a notable exception to this rule. Due to peculiarities in its vascular supply, particularly vulnerable at its proximal end, nondisplaced scaphoid fractures

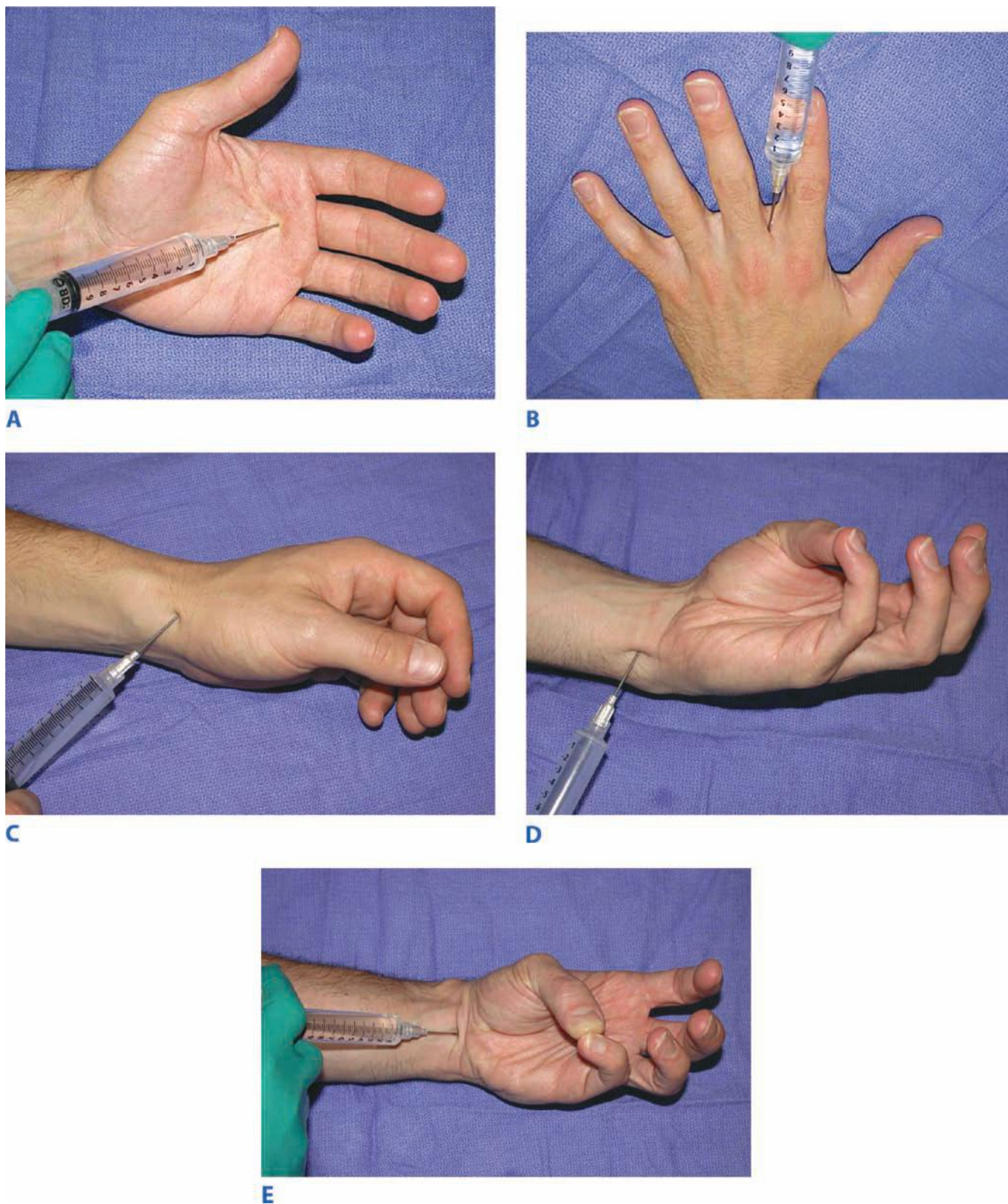


Figure 44-11. Local anesthesia can be administered at the digital or the wrist level. **A.** A single injection into the flexor tendon sheath at the metacarpal head level provides complete anesthesia for the digit. **B.** Alternatively, one can inject from a dorsal approach into the web space on either side. **C.** The superficial radial nerve is blocked by infiltrating subcutaneously over the distal radius from the radial artery pulse to the distal radioulnar joint. The dorsal sensory branch of the ulnar nerve is blocked in similar fashion over the distal ulna. **D.** To block the ulnar nerve, insert the needle parallel to the plane of the palm and deep to the flexor carpi ulnaris tendon; aspirate to confirm the needle is not in the adjacent ulnar artery. **E.** To block the median nerve, insert the needle just ulnar to the palmaris longus tendon into the carpal tunnel. One should feel two points of resistance: one when piercing the skin, the second when piercing the antebrachial fascia.

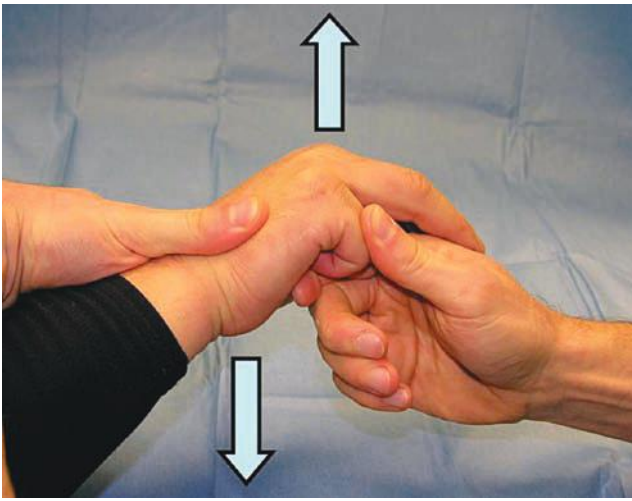


Figure 44-12. The Jahss maneuver. The surgeon fully flexes the patient's small finger into the palm and secures it in his distal hand. The proximal hand controls the wrist and places the thumb on the patient's fracture apex (the most prominent dorsal point). The examiner distracts the fracture, pushes dorsally with the distal hand (*up arrow*), and resists dorsal motion with the proximal hand (*down arrow*).

can fail to unite in up to 20% of patients even with appropriate immobilization. Recent developments in hardware and surgical technique have allowed stabilization of the fracture with minimal surgical exposure. One prospective randomized series of scaphoid wrist fractures demonstrated shortening of time to union by up to 6 weeks in the surgically treated group, but no difference in rate of union.¹² Surgery may be useful in the younger, more active patient who would benefit from an earlier return to full activity.

Ligament injuries of the wrist can be difficult to recognize. Patients often present late and may not be able to localize their pain. In severe cases, the ligaments of the wrist can rupture to the point of dislocation of the capitate off the lunate or even the lunate off the radius. Mayfield and colleagues classified the progression of this injury into four groups.¹³ In the most severe group, the lunate dislocates off the radius into the carpal tunnel. In some circumstances, the scapholunate ligament rupturing. Attention to the congruency or disruption of Gilula's arcs will help the examiner to recognize this injury. For patients with type 4 (most severe) and some with type 3 injury, the examiner should also evaluate for sensory disturbance in the median nerve distribution because this may indicate acute carpal tunnel syndrome and necessitate more urgent intervention. Although the Mayfield pattern of injury is most common, force can also transmit along alternate paths through the carpus.¹⁴

After reduction of fractures and dislocations (as well as after surgical repair of these and many other injuries), the hand must be splinted in a protected position. For the fingers, MP joints should be splinted 90°, and the IP joints at 0° (called the *intrinsic plus position*). The wrist is generally splinted at 20° extension because this puts the hand in a more functional position. This keeps the collateral ligaments on tension and helps prevent secondary contracture. In general, one of three splints should be used for the ER patient (Fig. 44-13). The ulnar gutter splint uses places plaster around the ulnar

border of the hand. It is generally appropriate for small finger injuries only. Dorsal plaster splints can be used for injuries of any of the fingers. Plaster is more readily contoured to the dorsal surface of the hand than the volar surface, particularly in the setting of trauma-associated edema. For thumb injuries, the thumb spica splint is used to keep the thumb radially and palmarly abducted from the hand.

Tendons

Injuries to the flexor and extensor tendons compromise the mobility and strength of the digits. On inspection, injury is normally suspected by loss of the normal cascade of the fingers. The patient should be examined as described earlier to evaluate for which tendon motion is deficient. If the patient is unable to cooperate, extension of the wrist will produce passive flexion of the fingers and also demonstrate a deficit. This is referred to as the tenodesis maneuver.

Flexor tendon injuries are described based on zones (Fig. 44-14). Up until 40 years ago, zone 2 injuries were always reconstructed and never repaired primarily due to concern that the bulk of repair within the flexor sheath would prevent tendon glide. The work of Dr. Kleinert and colleagues at the University of Louisville changed this "axiom" and established the principle of primary repair and early controlled mobilization postoperatively.¹⁵ Flexor tendon injuries should always be repaired in the operating room. Although they do not need to be repaired on the day of injury, the closer to the day of injury they are repaired, the easier it will be to retrieve the retracted proximal end in surgery. The laceration should be washed out and closed at the skin level only using permanent sutures. The hand should be splinted as described earlier; one notable difference is that the wrist should be splinted at slight flexion (about 20°) to help decrease the retracting force on the proximal cut tendon end.

Extensor tendons do not pass through a sheath in the fingers. As such, bulkiness of repair is less of a concern. With proper supervision/experience and equipment, primary extensor tendon repair can be performed in the ER.

Very distal extensor injuries near the insertion on the dorsal base of the distal phalanx may not have sufficient distal tendon to hold a suture. Closed injuries, called mallet fingers, can be treated with extension splinting of the DIP joint for 6 continuous weeks. For patients with open injuries, a dermatotendodesis suture is performed. A 2-0 or 3-0 suture is passed through the distal skin, tendon remnant, and proximal tendon as a mattress suture. Using a suture of a different color than the skin closing sutures will help prevent removing the dermatotendodesis suture(s) too soon. The DIP joint is splinted in extension.

More proximal injuries are typically repaired with a 3-0 braided permanent suture. Horizontal mattress or figure-of-eight sutures should be used, two per tendon if possible. Great care should be used to ensure matching the appropriate proximal and distal tendon ends. The patient is splinted with IP joints in extension and the wrist in extension per usual. MP joints should be splinted in 45° flexion, sometimes less. Although this position is not ideal for MP collateral ligaments, it is important for taking tension off of the tendon repairs.

Nerve Injuries

In the setting of a sharp injury, a sensory deficit implies a nerve laceration until proven otherwise. For blunt injuries, even displaced fractures and dislocations, nerves are often contused but not lacerated and are managed expectantly. Nerve repairs require



Figure 44-13. Commons splints used for hand injuries/surgeries. **A.** Ulnar gutter splint. The ring and small fingers are included. The surgeon pushes on the dorsum of the fingers with the distal hand to produce interphalangeal (IP) joint extension and metacarpophalangeal (MP) joint flexion to 90°, while the proximal hand controls wrist position. **B.** Dorsal four-finger splint. As with the ulnar gutter splint, finger MP joints are flexed to 90° with IP joints kept fully extended. **C.** Thumb spica splint. One easy method to fabricate is to place one slab of plaster radially over the wrist and thumb with a second square of plaster over the thenar eminence, which joins the first. In this patient, the IP joint was not included. For injuries at, or distal to, the MP joint, the IP should be included in the splint.

appropriate microsurgical equipment and suture; they should not be performed in the ER. As with tendons, nerve injuries do not require immediate exploration. However, earlier exploration will allow for easier identification of structures and less scar tissue to be present. The nerve must be resected back to healthy nerve fascicle prior to repair. Delay between injury and repair can thus make a difference between the ability to repair a nerve primarily or the need to use a graft. The injured hand should be splinted with MPs at 90° and IPs at 0°, as described earlier.

Vascular Injuries

Vascular injuries have the potential to be limb or digit threatening. A partial laceration of an artery at the wrist level can potentially cause exsanguinating hemorrhage. Consultations for these injuries must be evaluated urgently.

Initial treatment for an actively bleeding wound should be direct local pressure for no less than 10 continuous minutes. If this is unsuccessful, an upper extremity tourniquet inflated to 100 mmHg above the systolic pressure should be used. One should keep this tourniquet time to less than 2 hours to avoid tissue necrosis. Once bleeding is controlled well enough to evaluate the wound, it may be cautiously explored to evaluate

for bleeding points. One must be very cautious if attempting to ligate these to ensure that adjacent structures such as nerves are not included in the ligature.

The hand must be evaluated for adequacy of perfusion to the hand as a whole as well as the individual digits. Capillary refill, turgor, Doppler signal, and bleeding to pinprick all provide useful information regarding vascular status. The finger or hand with vascular compromise requires urgent operative exploration. Unlike the complete amputation, in which the amputated part can be cold preserved (see below), devascularization without amputation produces warm ischemia, which is tolerated only for a matter of hours.

For the noncritical vascular injury, two treatment options exist. Simple ligation will control hemorrhage. At least one of the palmar arterial arches is intact in 97% of patients,⁵ so this will usually not compromise hand perfusion. Each digit also has two arterial inflows and can survive on one (see Amputations and Replantation section below). In the academic hospital setting, however, consideration should be given to repairing all vascular injuries. Instructing a resident in vascular repair in the noncritical setting will produce a more skilled and prepared resident for when a critical vascular injury does arise.

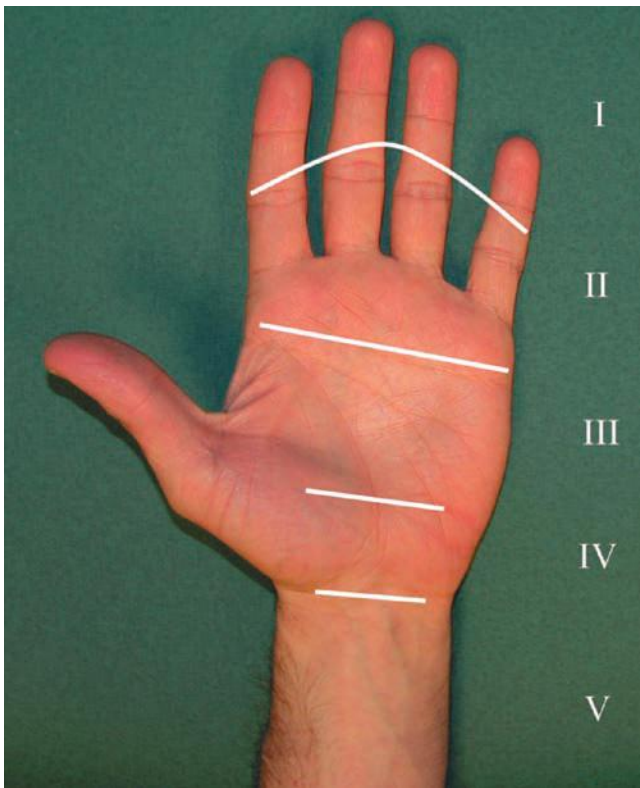


Figure 44-14. The zones of flexor tendon injury. *I.* Flexor digitorum superficialis insertion to the flexor digitorum profundus insertion. *II.* Start of the A1 pulley to the flexor digitorum superficialis insertion. *III.* End of the carpal tunnel to the start of the A1 pulley. *IV.* Within the carpal tunnel. *V.* Proximal to the carpal tunnel.

SPECIAL CONSIDERATIONS

Amputations and Replantation

After replantation was first reported,¹⁶ replantation was attempted for nearly all amputations. Over the ensuing decades, more stringent guidelines have been established regarding what should be replanted. Indications for replantation include amputations of the thumb, multiple digit amputations, and amputations in children. Relative contraindications to replantation include crush injuries, injuries to a single digit distal to the PIP joint, and patients who are unable to tolerate a long surgical procedure. As with all guidelines, one should evaluate the particular needs of the injured patient.

In preparation for replantation, the amputated part and proximal stump should be appropriately treated. The amputated part should be wrapped in moistened gauze and placed in a sealed plastic bag. This bag should then be placed in an ice water bath. Do not use dry ice, and do not allow the part to contact ice directly; frostbite can occur in the amputated part, which will decrease its chance of survival after replantation. Bleeding should be controlled in the proximal stump by as minimal a means necessary, and the stump should be dressed with a nonadherent gauze and bulky dressing.

For digital amputations deemed unsalvageable, revision amputation can be performed in the ER if appropriate equipment is available. Bony prominences should be smoothed off with a rongeur and/or rasp. Great care must be taken to identify the digital nerves and resect them back as far proximally in the wound as possible; this helps decrease the chance of painful

neuroma in the skin closure. Skin may be closed with permanent or absorbable sutures; absorbable sutures will spare the patient the discomfort of suture removal several weeks later. For more proximal unsalvageable amputations, revision should be performed in the operating room to maximize vascular and neural control.

Prostheses can be made for amputated parts. The more proximal the amputation, the more important to function the prosthesis is likely to be. Although finger-level prostheses are generally considered cosmetic, patients with multiple finger amputations proximal to the DIP have demonstrable functional benefit from their prosthesis as well.¹⁷

Fingertip Injuries

Fingertip injuries are among the most common pathologies seen in an ER. The usual history is that a door closed on the finger (commonly the middle, due to its increased length) or something heavy fell on the finger.

Initial evaluation should include: wound(s) including the nail bed, perfusion, sensation, and presence and severity of fractures. For the common scenario, complex lacerations with minimally displaced fracture(s) and no loss of perfusion, the wound is cleansed, sutured, and splinted in the ER. To properly assess the nail bed, the nail plate (hard part of the nail) should be removed. A Freer periosteal elevator is well suited for this purpose. Lacerations are repaired with 6-0 fast gut suture. Great care must be taken when suturing because excessive traction with the needle can further lacerate the tissue. After repair, the nail folds are splinted with the patient's own nail plate (if available) or with aluminum foil from the suture pack. This is done to prevent scarring from the nail folds down to the nail bed that would further compromise healing of the nail.

In some situations, tissue may have been avulsed in the injury and be unavailable for repair. Choice of treatment options depends on the amount and location of tissue loss (Fig. 44-15).

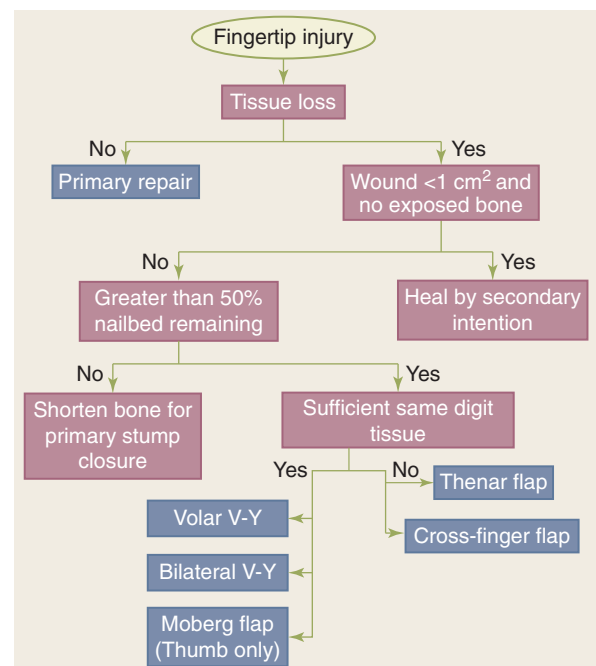


Figure 44-15. Treatment algorithm for management of fingertip injuries. See text for description of flaps.

For wounds less than 1 cm² with no exposed bone, secondary intention will produce excellent functional and aesthetic results. For larger wounds or wounds with bone exposed, one must decide if the finger is worth preserving at the current length or if shortening to allow for primary closure is a better solution. A useful guideline is the amount of fingernail still present; if greater than 50% is present, local or regional flap coverage may be a good solution.

If sufficient local tissue is present, homodigital flaps can be considered. A wide range of antegrade and retrograde homodigital flaps can be mobilized to cover the defect. Some carry sensation or can receive nerve coaptation to recover sensation over time.¹⁸ For the thumb only, the entire volar skin including both neurovascular bundles can be raised and advanced distally up to 1.5 cm.¹⁹ The thumb receives separate vascularity to its dorsal skin from the radial artery. This flap is not appropriate for the fingers. Patients retain full sensibility in the advanced skin and can be mobilized within days of surgery (Fig. 44-16A–C).

For wounds too large to cover with homodigital tissue, regional flaps can be considered. The skin from the distal radial thenar eminence can be raised as a random pattern flap (Fig. 44-16D–F). The finger is maintained in flexion for 14 to 21 days until division of the flap pedicle and inset of the flap. Some authors have reported prolonged stiffness in patients over 30 years old, but careful flap design helps minimize this complication.²⁰ Alternatively, the skin from the dorsum of the middle phalanx of an adjacent digit can be raised as a flap to cover the volar P3 (Fig. 44-16G–I). The flap is inset at 14 to 21 days. Long-term studies have shown this flap develops sensation over time.²¹

Patients with fingertip injuries must be assessed for the possibility of salvage of the injured digit(s) taken within the context of the patient's recovery needs and goals. The surgeon then matches the available options to the particular patient needs.

High-Pressure Injection Injuries

High-pressure devices are commonly used for cleaning and applications of liquids such as lubricants and paint. Most commonly, the inexperienced worker accidentally discharges the device into his nondominant hand at the base of the digit. Severity of injury depends on the amount and type of liquid injected; hydrophobic compounds cause greater damage.

These injuries are typically quite innocuous to inspection. They are, however, digit-threatening emergencies. The patient should be informed of the severity of the injury, and exploration is ideally performed within 6 hours of injury. Up to 50% of such injuries result in loss of the digit, but early recognition and treatment are associated with increased chance of digit survival.²² Early frank discussion with the patient and initiation of appropriate treatment produce the best results and medicolegal protection.

Compartment Syndromes

Compartment syndromes can occur in the forearm and/or the hand. As in other locations, these are potentially limb-threatening issues. Principle symptoms are pain in the affected compartments, tense swelling, tenderness to palpation over the compartment, and pain with passive stretch of the muscles of the compartment.²³ Pulse changes are a late finding; normal pulses do not rule out compartment syndrome.

There are three compartments in the forearm and four groups of compartments in the hand. The volar forearm is one

compartment. On the dorsum of the forearm, there is the dorsal compartment as well as the mobile wad compartment, beginning proximally over the lateral epicondyle. In the hand, the thenar and hypothenar eminences each represent a compartment. The seven interosseous muscles each behave as a separate compartment.

Compartment syndrome can be caused by intrinsic and extrinsic causes. Intrinsic causes include edema and hematoma due to fracture. Extrinsic causes include splints and dressings that are circumferentially too tight and intravenous infiltrations. Infiltrations with hyperosmolar fluids such as x-ray contrast are particularly dangerous, because additional water will be drawn in to neutralize the hyperosmolarity.

Measurement of compartment pressures can be a useful adjunct to assessment of the patient. The Stryker pressure measurement device or similar device is kept in many operating rooms for this purpose. The needle is inserted into the compartment in question, a gentle flush with 0.1 to 0.2 cc of saline clears the measurement chamber, and a reading is obtained. Studies have disagreed about whether the criterion is a measured pressure (30–45 mmHg, depending on the series) or within a certain amount of the diastolic blood pressure.²⁴

Compartment releases are performed in the operating room under tourniquet control. Release of the volar forearm compartment includes release of the carpal tunnel. As the incision travels distally, it should pass ulnar and then curve back radially just before the carpal tunnel. This avoids a linear incision across a flexion crease and also decreases the chance of injury to the palmar cutaneous branch of the median nerve. One dorsal forearm incision can release the dorsal compartment and the mobile wad. In the hand, the thenar and hypothenar compartments are released each with a single incision. The interosseous compartments are released with incisions over the index and ring metacarpal shafts. Dissection then continues radial and ulnar to each of these bones and provides release of all the muscle compartments. Any dead muscle is debrided. Incisions are left open and covered with a nonadherent dressing. The wounds are reexplored in 2 to 3 days to assess for muscle viability. Often the incisions can be closed primarily, but a skin graft may be needed for the forearm.

If the examiner feels the patient does not have a compartment syndrome, elevation and serial examination are mandatory. When in doubt, it is safer to release an early compartment syndrome than wait to release and risk muscle necrosis. Progression of compartment syndrome can lead to Volkmann's ischemic contracture with muscle loss and scarring that may compress nerves and other critical structures. Medicolegally, it is far easier to defend releasing an early compartment syndrome than delaying treatment until the process has progressed to necrosis and/or deeper scarring.

COMPLICATIONS

Nonunion

Any fractured bone has the risk of failing to heal. Fortunately, in the fingers and hand, this is a rare problem. Tuft injuries, where soft tissue interposes between the fracture fragments, have relatively higher risk of this problem. The nonunion tuft can be treated with débridement and bone grafting or revision amputation depending on the needs and goals of the patient. Phalangeal and metacarpal nonunions are also quite rare. They can similarly be treated with débridement of the nonunion, grafting,



A



B

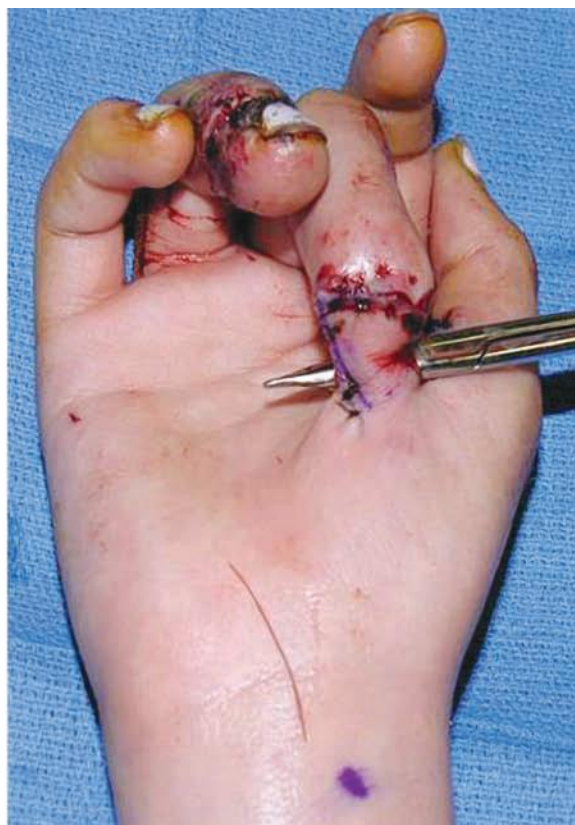


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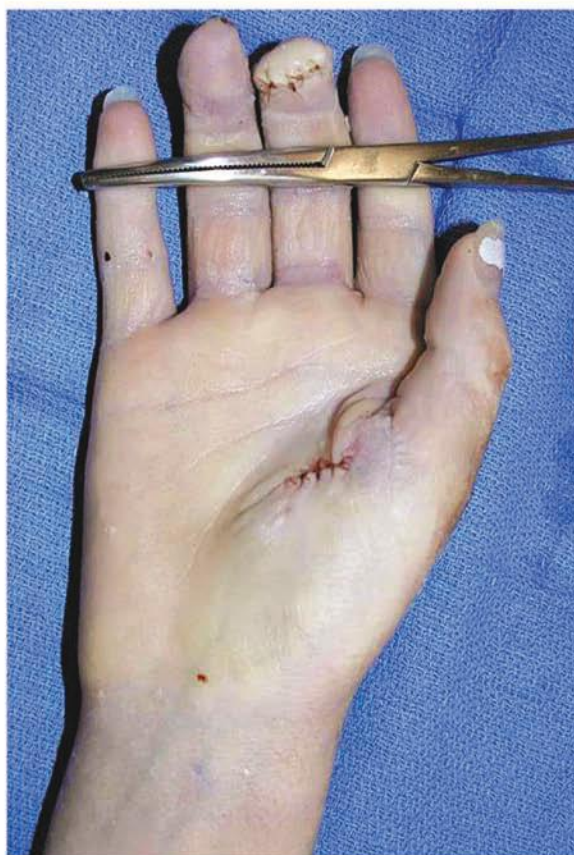
Figure 44-16. Local flaps for digital tip coverage. **A–C.** For thumb injuries, Moberg described elevation of the entire volar skin with both neurovascular bundles for distal advancement. Sensation to the advanced skin is maintained. **D–F.** An 8-year-old girl underwent fingertip replantation that did not survive. A thenar flap was transferred to cover the defect. Some authors advise against its use in patients over 30 years old. **G–I.** In this 45-year-old man, the entire skin of P3 of the long finger was avulsed and unrecoverable. A cross-finger flap was transferred and provides excellent, durable coverage. The border of the flap and surrounding skin is still apparent 4.5 months after surgery.



D



E



F

Figure 44-16 (Continued)



G



H



I

Figure 44-16 (Continued)

and rigid fixation.²⁵ More proximally, the scaphoid bone of the wrist has a significant risk of nonunion even if nondisplaced (see Fig. 44-9A). Any patient suspected of a scaphoid injury, namely those with tenderness at the anatomic snuffbox, should be placed in a thumb spica splint and reevaluated within 2 weeks even if initial X-rays show no fracture. Scaphoid nonunions can be quite challenging to repair,²⁶ and immobilization at the time of injury in a thumb spica splint is essentially always warranted.

Stiffness

The desired outcome of any hand injury is a painless, mobile, functional hand. Multiple factors can contribute to decreased mobility, including complex injuries of soft tissue and bone, noncompliance of the patient with postoperative therapy, and inappropriate splinting. The surgeon performing the initial evaluation can greatly impact this last factor. The goal of splinting is to keep the collateral ligaments on tension (MPs at 90°, IP joints straight). For severe cases of stiffness, mobilization surgeries such as tenolysis and capsulotomies²⁷ can be performed, but these rarely produce normal range of motion. Prevention of joint contractures with appropriate splinting and early, protected mobilization is the best option to maximize mobility at the end of healing. Healing of an injured or diseased structure in the hand is not the endpoint of treatment; the goal of any intervention must be to obtain structure healing, relief of pain, and maximization of function.

Neuroma

Any lacerated nerve will form a neuroma. A neuroma consists of a ball of scar and axon sprouts at the end of the injured nerve.²⁸ In unfavorable circumstances, this neuroma can become painful. The SRN is particularly notorious for this problem. By providing proximal axon sprouts a target, nerve repair is an excellent preventive technique. In some circumstances, such as injuries requiring amputation, this is not possible. As mentioned earlier, the surgeon should resect the nerve stump as far proximally in the wound as possible to avoid the nerve stump healing in the cutaneous scar to minimize this risk.

For the patient who develops a painful neuroma, nonsurgical treatments are initiated first. The neuroma can be identified by the presence of a Tinel's sign. Therapy techniques of desensitization, ultrasound, and electrical stimulation have all proven useful. Corticosteroid injection to the neuroma has also proven useful in some hands.

When these techniques fail, surgery is contemplated. The neuroma can be resected, but a new one will form to replace it. The nerve ending can be buried in muscle or even bone to prevent the neuroma from residing in a superficial location where it may be impacted frequently.

Regional Pain Syndromes

Injuries to the upper extremity can occasionally result in the patient experiencing pain beyond the area of initial injury. Reflex sympathetic dystrophy and sympathetic mediated pain are two terms that have been used in the past to describe this phenomenon. Both are inaccurate, as the sympathetic nervous system is not always involved. Current terminology for this condition is complex regional pain syndrome (CRPS). Type I occurs in the absence of a documented nerve injury; type II occurs in the presence of one.²⁹

CRPSs manifest as pain beyond the area of initial injuries. There is often associated edema and changes in hair and/or sweat distribution. Comparison to the unaffected side

is useful to better appreciate these findings. There are currently no imaging studies that can be considered diagnostic for CRPS.³⁰

For the patient in whom the diagnosis of CRPS is not clear, no definitive diagnostic study exists. Patients suspected of CRPS should be referred for aggressive hand therapy. Brief trials of oral corticosteroids have been successful in some series. Referral to a pain management specialist including a trial of stellate ganglion blocks is also frequently employed.

NERVE COMPRESSION

Nerves conduct signals along their axonal membranes toward their end organs. Sensory axons carry signals from distal to proximal; motor axons from proximal to distal. Myelin from Schwann cells allows faster conduction of signals. Signals jump from the start of one Schwann cell to the end of the cell (a location called a gap junction) and only require the slower membrane depolarization in these locations.

Nerve compression creates a mechanical disturbance of the nerve.³¹ In early disease, the conduction signal is slowed across the area of compression. When compression occurs to a sufficient degree for a sufficient time, individual axons may die. On a nerve conduction study, this manifests as a decrease in amplitude. Muscles receiving motor axons may show electrical disturbance on electromyogram (EMG) when sufficiently deprived of their axonal input.

Compression of sensory nerves typically produces a combination of numbness, paresthesias (pins and needles), and pain. Knowledge of the anatomic distribution of the peripheral nerves can aid in diagnosis. Sensory disturbance outside an area of distribution of a particular nerve (e.g., volar and dorsal radial-sided hand numbness for median nerve) makes compression of that nerve less likely. Diseases that cause systemic neuropathy (e.g., diabetes) can make diagnosis more difficult.

Nerve compression can theoretically occur anywhere along a peripheral nerve's course. The most common sites of nerve compression in the upper extremity are the median nerve at the carpal tunnel, ulnar nerve at the cubital tunnel, and ulnar nerve at Guyon's canal. Other, less common locations of nerve compression are described as well. In addition, a nerve can become compressed in scar due to a previous trauma.

Carpal Tunnel Syndrome

The most common location of upper extremity nerve compression is the median nerve at the carpal tunnel, called carpal tunnel syndrome (CTS). The carpal tunnel is bordered by the scaphoid bone radially, the lunate and capitate bones dorsally, and the hook of the hamate bone ulnarly (see Fig. 44-3). The transverse carpal ligament, also called the flexor retinaculum, is its superficial border. The FPL, four FDS, and four FDP tendons pass through the carpal tunnel along with the median nerve. Of these 10 structures, the median nerve is relatively superficial and radial to the other nine.

An estimated 53 per 10,000 working adults have evidence of CTS. The National Institute for Occupational Safety and Health website asserts, "There is strong evidence of a positive association between exposure to a combination of risk factors (e.g., force and repetition, force and posture) and CTS."³² There is disagreement among hand surgeons regarding whether occurrence of CTS in a patient who does repetitive activities at work represents a work-related injury.

Initial evaluation of the patient consists of symptom inventory: location and character of the symptoms, sleep disturbance due to symptoms, history of dropping objects, and difficulty manipulating small objects such as buttons, coins, or jewelry clasps.

Physical examination should begin with inspection. Look for evidence of wasting of the thenar muscles. Tinel's sign should be tested over the median nerve from the volar wrist flexion crease to the proximal palm, although this test has significant interexaminer variability.³³ Applying pressure over the carpal tunnel while flexing the wrist has been shown in one series to have the highest sensitivity when compared to Phalen's and Tinel's signs.³⁴ Strength of the thumb in opposition should also be tested.

Early treatment of CTS consists of conservative management. The patient is given a splint to keep the wrist at 20° extension worn at nighttime. Many patients can have years of symptom relief with this management. As a treatment and diagnostic modality, corticosteroid injection of the carpal tunnel is often employed. Mixing local anesthetic into the solution provides the benefit of early symptom relief (corticosteroids often take 3–7 days to provide noticeable benefit), and report of postinjection anesthesia in the median nerve distribution confirms the injection went into the correct location. Multiple authors have shown a strong correlation to relief of symptoms with corticosteroid injection and good response to carpal tunnel release.³⁵

When lesser measures fail or are no longer effective, carpal tunnel release is indicated. Open carpal tunnel release is a time-tested procedure with documented long-term relief of symptoms. A direct incision is made over the carpal tunnel, typically in line with where the ring finger pad touches the proximal palm in flexion. Skin is divided followed by palmar fascia. The carpal tunnel contents are visualized as they exit the carpal tunnel. The transverse carpal ligament is divided with the median nerve visualized and protected at all times. Improvement in symptoms is typically noted by the first postoperative visit, although symptom relief may be incomplete for patients with long-standing disease or systemic nerve-affecting diseases such as diabetes.

Endoscopic techniques have been devised to address CTS. All involve avoidance of incising the skin directly over the carpal tunnel. In experienced hands, endoscopic carpal tunnel release provides the same relief of CTS with less intense and shorter lasting postoperative pain. After 3 months, however, the results are equivalent to open release.³⁶ In inexperienced hands, there may be a higher risk of injury to the median nerve with the endoscopic techniques; this procedure is not for the occasional carpal tunnel surgeon.

Cubital Tunnel Syndrome

The second most common location of upper extremity nerve compression is the ulnar nerve where it passes behind the elbow at the cubital tunnel. The cubital tunnel retinaculum passes between the medial epicondyle of the humerus and the olecranon process of the ulna. It stabilizes the ulnar nerve in this location during elbow motion. Over time, or sometimes after trauma, the ulnar nerve can become less stabilized in this area. Motion of the elbow then produces trauma to the nerve as it impacts the retinaculum and medial epicondyle.

Cubital tunnel syndrome may produce sensory and motor symptoms.³⁷ The small finger and ulnar half of the ring fingers

may have numbness, paresthesias, and/or pain. The ulnar nerve also innervates the dorsal surface of the small finger and ulnar side of the ring finger, so numbness in these areas can be explained by cubital tunnel syndrome. The patient may also report weakness in grip due to effects on the FDP tendons to the ring and small fingers and the intrinsic hand muscles. Patients with advanced disease may complain of inability to fully extend the ring and small finger IP joints.

Physical examination for cubital tunnel syndrome begins with inspection. Look for wasting in the hypothenar eminence and the interdigital web spaces. When the hand rests flat on the table, the small finger may rest in abduction with respect to the other fingers; this is called Wartenberg's sign. Tinel's sign is often present at the cubital tunnel. Elbow flexion test will often be positive. Grip strength and finger abduction strength should be compared to the unaffected side. Froment's sign can be tested by placing a sheet of paper between the thumb and index finger and instructing the patient to hold on to the paper while the examiner pulls it away without flexing the finger or thumb (this tests the strength of the adductor pollicis and first dorsal interosseous muscles). If the patient must flex the index finger and/or thumb (FDP-index and FPL, both median nerve supplied) to maintain traction on the paper, this is a positive response.

Early treatment of cubital tunnel syndrome begins with avoiding maximal flexion of the elbow. Splints are often used for this purpose. Corticosteroid injection is rarely done for this condition; unlike in the carpal tunnel, there is very little space within the tunnel outside of the nerve. Injection in this area runs a risk of intraneural injection, which can cause permanent scarring of the nerve and dysfunction.

When conservative management fails, surgery has been contemplated. Treatment options include releasing the cubital tunnel retinaculum with or without transposing the nerve anterior to the elbow. While some authors advocate anterior transposition into the flexor-pronator muscle group with the goal of maximizing nerve recovery,³⁷ recent studies have demonstrated equivalent results between transposition and in situ release of the nerve even in advanced cases.³⁸ For this reason, the simpler in situ release, either open or endoscopic, is preferred by many surgeons.

Other Sites of Nerve Compression

All nerves crossing the forearm have areas described where compression can occur.³⁷ The median nerve can be compressed as it passes under the pronator teres. The ulnar nerve can be compressed as it passes through Guyon's canal. The radial nerve, or its posterior interosseous branch, can be compressed as it passes through the radial tunnel (distal to the elbow where the nerve divides and passes under the arch of the supinator muscle). The SRN can be compressed distally in the forearm as it emerges from under the brachioradialis tendon, called Wartenberg's syndrome. As mentioned previously, any nerve can become compressed in scar at the site of a previous trauma.

DEGENERATIVE JOINT DISEASE

As with other joints in the body, the joints of the hand and wrist can develop degenerative changes. Symptoms typically begin in the fifth decade of life. Symptoms consist of joint pain and stiffness and often are exacerbated with changes in the weather. Any of the joints can become involved. As the articular cartilage wears out, pain typically increases and range of motion

decreases. The patient should always be asked to what degree symptoms are impeding activities.

Physical findings are documented in serial fashion from the initial visit and subsequent visits. Pain with axial loading of the joint may be present. Decreased range of motion may be a late finding. Instability of the collateral ligaments of the joint is uncommon in the absence of inflammatory arthritis.

Plain X-rays are typically sufficient to demonstrate arthritis. Initially, the affected joint has a narrower radiolucent space between the bones. As joint degeneration progresses, the joint space further collapses. Bone spurs, loose bodies, and cystic changes in the bone adjacent to the joint all may become apparent. X-ray findings do not always correlate with patient symptoms. Patients with advanced x-ray findings may have minimal symptoms, and vice versa. Treatment is initiated and progressed based on the patient's symptoms regardless of imaging findings.

Initial management begins with rest of the painful joint. Splints are often useful, but may significantly impair the patient in activities and thus are frequently used at nighttime only. Oral nonsteroidal anti-inflammatory medications such as ibuprofen and naproxen are also useful. Patients on anticoagulants and antiplatelet medications may not be able to take these, and some patients simply do not tolerate the gastric irritation side effect even if they take the medication with food.

For patients with localized disease affecting only one or a few joints, corticosteroid injection may be contemplated. Needle insertion can be difficult since these joint spaces are quite narrow even before degenerative disease sets in. Also, many corticosteroid injections are suspensions, not solutions; injected corticosteroid will remain in the joint space and can be seen as a white paste if surgery is performed on a joint that has been previously injected.

Small Joints (Metacarpophalangeal and Interphalangeal)

When conservative measures fail, two principal surgical options exist: arthrodesis and arthroplasty. The surgeon and patient must decide together as to whether conservative measures have failed. Surgery for arthritis, whether arthrodesis or arthroplasty, is performed for the purpose of relieving pain. Arthrodesis, fusion of a joint, provides excellent relief of pain and is durable over time. However, it comes at the price of total loss of motion.

Silicone implant arthroplasty has been available for over 40 years.³⁹ Rather than a true replacement of the joint, the silicone implant acts as a spacer between the two bones adjacent to the joint. This allows for motion without bony contact that would produce pain. Long-term studies have shown that all implants fracture over time, but usually continue to preserve motion and pain relief.⁴⁰

In the past 15 years, resurfacing implant arthroplasties have become available for the small joints of the hand. Multiple different materials have been used to fabricate such implants. These are designed to behave as a true joint resurfacing (as knee and hip arthroplasty implants are) and have shown promising outcomes in short- and intermediate-term studies.⁴⁰ Neither the silicone nor the resurfacing arthroplasties preserve (or restore) full motion of the MP or PIP joints.

Wrist

The CMC joint of the thumb, also called the basilar joint, is another common location of arthritis pain. Pain in this joint particularly disturbs function because the CMC joint is essential for

opposition and cylindrical grasp. Patients will typically complain of pain with opening a tight jar or doorknob and strong pinch activities such as knitting. Conservative management is used first, as described earlier. Prefabricated, removable thumb spica splinting can provide excellent relief of symptoms for many patients.

Multiple surgical options exist for thumb CMC arthritis. Many resurfacing implants have been used in the past; often they have shown good short- and intermediate-term results and poor long-term results. Resection of the arthritic trapezium provides excellent relief of pain; however, most authors feel that stabilization of the thumb metacarpal base is necessary to prevent shortening and instability.⁴¹ Recently, one author demonstrated excellent long-term results from resection of the trapezium without permanent stabilization of the metacarpal base.⁴² For both of these operations, the thumb base may not be sufficiently stable to withstand heavy labor. For these patients, fusion of the thumb CMC in mild opposition provides excellent pain relief and durability. The patient must be warned preoperatively that he will not be able to lay his hand flat after the surgery. This loss of motion can be problematic when the patient attempts to tuck in clothing or reach into a narrow space.

Degenerative change of the radiocarpal and midcarpal joints is often a consequence of scapholunate ligament injury. Often the initial injury goes untreated, with the patient believing it is merely a "sprain"; the patient is first diagnosed with the initial injury when he presents years later with degenerative changes.

Degenerative wrist changes associated with the scapholunate ligament follow a predictable pattern over many years, called *scapholunate advanced collapse* or *SLAC wrist*.⁴³ Because of this slow progression (Fig. 44-17A), patients can usually be treated with a motion-sparing procedure. If there is truly no arthritic change present, the scapholunate ligament can be reconstructed.

If arthritis is limited to the radiocarpal joint, two motion-sparing options are available. The proximal carpal row (scaphoid, lunate, and triquetrum) can be removed (proximal row carpectomy [PRC]). The lunate facet of the radius then articulates with the base of the capitate, whose articular surface is similar in shape to that of the base of the lunate. Most series show maintenance of about 66% of wrist motion and 66% of hand strength or more, as compared to the opposite side.⁴⁴ Alternatively, the scaphoid can be excised, and four-bone fusion (lunate, capitate, hamate, and triquetrum) can be performed. This maintains the full length of the wrist and the lunate in the lunate facet of the radius. Some series have shown better strength but less mobility with this technique, others have shown equivalent results to the PRC.⁴⁵ The four-bone fusion does appear to be more durable for younger patients and/or those who perform heavy labor.

If the patient presents with pancarpal arthritis or motion-sparing measures have failed to alleviate pain, total wrist fusion is the final surgical option. The distal radius is fused, through the proximal and distal carpal rows to the third metacarpal, typically with a dorsal plate and screws. Multiple long-term studies have shown excellent pain relief and durability; this comes at the cost of total loss of wrist motion. This is surprisingly well tolerated in most patients, especially if the other hand/wrist is unaffected. The only activity of daily living that cannot be done with a fused wrist is personal toileting.



A



B

Figure 44-17. Arthritis of the hand and wrist. **A.** This patient injured her scapholunate ligament years prior to presentation. The scapholunate interval is widened (*double arrow*), and the radioscaphoid joint is degenerated (*solid oval*), but the radiolunate and lunocapitate joint spaces are well preserved (*dashed ovals*). **B.** This patient has had rheumatoid arthritis for decades. The classic volar subluxation of the metacarpophalangeal joints of the fingers (*dashed oval*) and radial deviation of the fingers are apparent.

Rheumatoid Arthritis

Rheumatoid arthritis (RA) is an inflammatory arthritis that can affect any joint in the body. Inflamed synovium causes articular cartilage breakdown with pain and decreased range of motion. The goals of hand surgery for the RA patient are relief of pain, improvement of function, slowing progression of disease, and improvement in appearance.⁴⁶ In addition, swelling of the joint due to the inflammation can cause laxity and even failure of the collateral ligaments supporting the joints. Recent advances in

the medical care of RA have made the need for surgical care of these patients far less common than in previous decades.

MP joints of the fingers are commonly affected. The base of the proximal phalanx progressively subluxates and eventually dislocates volarly with respect to the metacarpal head. The collateral ligaments, particularly on the radial side, stretch out and cause the ulnar deviation of the fingers characteristic of the rheumatoid hand. In more advanced cases, the joint may not be salvageable (Fig. 44-17B). For these patients, implant arthroplasty is the mainstay of surgical treatment. Silicone implants have been used for over 40 years with good results.⁴⁷ The silicone implant acts as a spacer between proximal and distal bone, rather than as a true resurfacing arthroplasty. The radial collateral ligament must be repaired to appropriate length to correct the preoperative ulnar deviation of the MP joint. Extensor tendon centralization is then performed, as needed, at the end of the procedure.

For MP joint and PIP joint disease, fusion is an option. However, since RA usually affects multiple joints, fusion is typically avoided due to impaired function of adjacent joints, which would leave a severe motion deficit to the finger.

Failure of the support ligaments of the distal radioulnar joint (DRUJ) leads to the *caput ulnae* posture of the wrist with the ulnar head prominent dorsally. As this dorsal prominence becomes more advanced, the ulna head, denuded of its cartilage to act as a buffer, erodes into the overlying extensor tendons. Extensor tenosynovitis, followed ultimately by tendon rupture, begins ulnarly and proceeds radially. Rupture of the ECU tendon may go unnoticed due to the intact ECRL and ECRB tendons to extend the wrist. EDQ rupture may go unnoticed if a sufficiently robust EDC tendon to the small finger exists. Once the fourth compartment (EDC) tendons begin to fail, the motion deficit is unable to be ignored by the patient.

Surgical solutions must address the tendon ruptures as well as the DRUJ synovitis and instability and ulna head breakdown that led to them.⁴⁶ Excision of the ulna head removes the bony prominence. The DRUJ synovitis must also be resected. Alternatively, the DRUJ can be fused and the ulna neck resected to create a pseudoarthrosis to allow for rotation. For both procedures, the remaining distal ulna must be stabilized. Multiple techniques have been described using portions of FCU, ECU, wrist capsule, and combinations thereof.

The ruptured extensor tendons are typically degenerated over a significant length. Primary repair is almost never possible, and the frequent occurrence of multiple tendon ruptures makes repair with graft less desirable due to the need for multiple graft donors.

Strict compliance with postoperative therapy is essential to maximizing the surgical result. Due to the chronic inflammation associated with RA, tendon and ligament repairs will be slower to achieve maximal tensile strength. Prolonged nighttime splinting, usually for months, helps prevent recurrence of extensor lag. Finally, the disease may progress over time. Reconstructions that were initially adequate may stretch out or fail over time. Medical management is the key to slowing disease progression and maximizing the durability of any surgical reconstruction.

DUPUYTREN'S CONTRACTURE

In 1614, a Swiss surgeon named Felix Plater first described contracture of multiple fingers due to palpable, cord-like structures on the volar surface of the hand and fingers. The disease state he described would ultimately come to be known as Dupuytren's

contracture. Dupuytren's name came to be associated with the disease after he performed an open fasciotomy of a contracted cord before a class of medical students in 1831.⁴⁸

The palmar fascia consists of collagen bundles in the palm and fingers. These are primarily longitudinally oriented and reside as a layer between the overlying skin and the underlying tendons and neurovascular structures. There are also connections from this layer to the deep structures below and the skin above. Much is known about the progression of these structures from their normal state (called bands) to their contracted state (called cords), but little is known on how or why this process begins.

Increased collagen deposition leads to a palpable nodule in the palm. Over time, there is increased deposition distally into the fingers. This collagen becomes organized and linearly oriented. These collagen bundles, with the aid of myofibroblasts, contract down to form the cords, which are the hallmark of the symptomatic patient. Detail of the molecular and cell biology of Dupuytren's disease is beyond the scope of this chapter but is available in multiple hand surgery texts.⁴⁹

Most nonoperative management techniques will not delay the progression of disease. Corticosteroid injections may soften nodules and decrease the discomfort associated with them but are ineffective against cords. Splinting has similarly been shown not to retard disease progression.

Disruption of the cord with a needle is an effective means of releasing contractures, particularly at the MP joint level. Long-term studies have demonstrated more rapid recovery from needle fasciotomy, as the procedure is called, but more durable results with fasciectomy.⁵⁰ Injectable clostridial collagenase was approved by the U.S. Food and Drug Administration in 2009 and shows good early results.⁵¹

For patients with advanced disease including contractures of the digits that limit function, surgery is the mainstay of therapy. Although rate of progression should weigh heavily in the decision of whether or not to perform surgery, general guidelines are MP contractures $\geq 30^\circ$ and/or PIP contractures $\geq 20^\circ$.⁵²

Surgery consists of an open approach through the skin down to the involved cords. Skin is elevated off of the underlying cords. Great care must be taken to preserve as much of the subdermal vascular plexus with the elevated skin flaps to minimize postoperative skin necrosis. All nerves, tendons, and blood vessels in the operative field should be identified. Once this is done, the involved cord is resected while keeping the critical deeper structures under direct vision. Skin is then closed, with local flap transpositions as needed, to allow for full extension of the fingers that have been released (Fig. 44-18).

Alternative cord resection techniques include removal of the skin over the contracture (dermatofasciectomy). This requires a skin graft to the wound and should only be done if skin cannot be separated from the cords and local tissue cannot be rearranged with local flaps to provide closure of the wound.

Complications of surgical treatment of Dupuytren's disease occur in as many as 24% of cases.⁵³ Problems include digital nerve laceration, digital artery laceration, buttonholing of the skin, hematoma, swelling, and pain, including some patients with CRPS (see earlier section on CRPS). Digital nerve injury can be quite devastating, producing annoying numbness at best or a painful neuroma in worse situations.

Hand therapy is typically instituted within a week of surgery to begin mobilization of the fingers and edema control. The therapist can also identify any early wound problems because

he or she will see the patient more frequently than the surgeon. Extension hand splinting is maintained for 4 to 6 weeks, with nighttime splinting continued for an additional 6 to 8 weeks. After this point, the patient is serially followed for evidence of recurrence or extension of disease.

INFECTIONS

Trauma is the most common cause of hand infections. Other predisposing factors include diabetes, neuropathies, and immunocompromised patients. Proper treatment consists of incision and drainage of any collections followed by débridement, obtaining wound cultures, antibiotic therapy, elevation, and immobilization. *Staphylococcus* and *Streptococcus* are the offending pathogens in about 90% of hand infections. Infections caused by intravenous drug use or human bites and those associated with diabetes will often be polymicrobial, including gram-positive and gram-negative species. Heavily contaminated injuries require anaerobic coverage. Although α -hemolytic *Streptococcus* and *Staphylococcus aureus* are the most commonly encountered pathogens in human bites, *Eikenella corrodens* is isolated in up to one-third of cases and should be considered when choosing antimicrobial therapy. Ziehl-Neelsen staining and cultures at 28°C to 32°C in Lowenstein-Jensen medium must be performed if there is a suspicion for atypical mycobacteria.⁵⁴

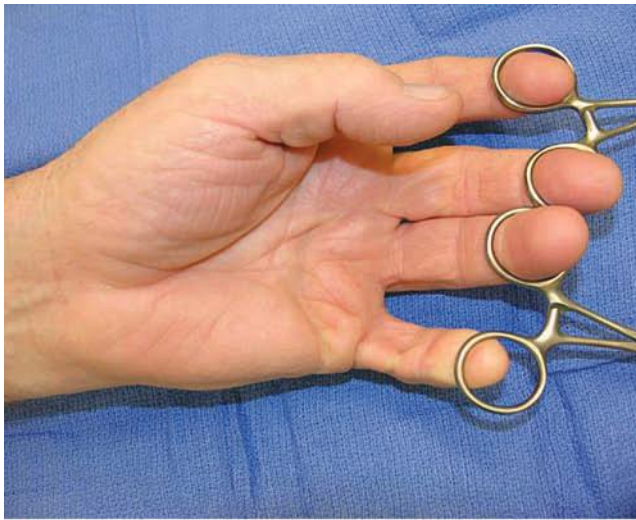
Cellulitis

Cellulitis is characterized by a nonpurulent diffuse spreading of inflammation characterized by erythema, warmth, pain, swelling, and induration. Skin breakdown is a frequent cause, but often no inciting factor is identified. Group A β -hemolytic *Streptococcus* is the most common offending pathogen and causes a more diffuse spread of infection. *S. aureus* is the second most common offending pathogen and will cause a more localized cellulitis. The diagnosis of cellulitis is clinical. Septic arthritis, osteomyelitis, an abscess, a deep-space infection, and necrotizing fasciitis are severe infectious processes that may initially mimic cellulitis. These must be ruled out appropriately before initiating treatment, and serial exams should be conducted to ensure proper diagnosis. Treatment of cellulitis consists of elevation, splint immobilization, and antibiotics that cover both *Streptococcus* and *Staphylococcus*.

5► Intravenous antibiotics are usually initiated for patients with severe comorbidities and those who fail to improve on oral antibiotics after 24 to 48 hours. Failure to improve after 24 hours indicates a need to search for an underlying abscess or other infectious cause.⁵⁴

Abscess

An abscess will present much like cellulitis, but they are two clinically separate entities. The defining difference is an area of fluctuance. Skin-puncturing trauma is the most common cause. *S. aureus* is the most common pathogen, followed by *Streptococcus*. Treatment consists of incision and drainage with appropriate débridement, wound cultures, wound packing, elevation, immobilization, and antibiotics. The packing should be removed in 12 to 24 hours or sooner if there is clinical concern, and warm soapy water soaks with fresh packing should be initiated. Most should be allowed to heal secondarily. Delayed primary closure should only be performed after repeat washouts for larger wounds where complete infection has been achieved.



A



B



C

Figure 44-18. Dupuytren's disease. **A.** This patient has cords affecting the thumb, middle, ring, and small fingers. **B.** The resected specimens are shown. **C.** Postoperatively, the patient went on to heal all his incisions and, with the aid of weeks of hand therapy, recover full motion.

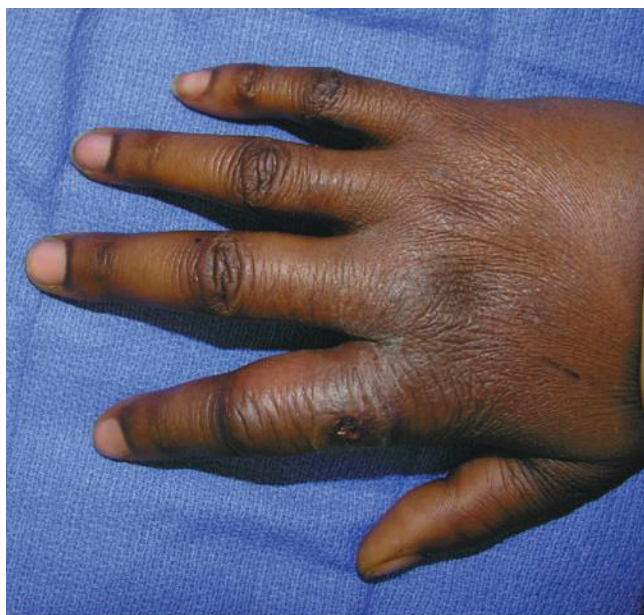
Collar-Button Abscess

This is a subfascial infection of a web space and is usually caused by skin trauma that becomes infected; it often occurs in laborers. The adherence of the palmar web space skin to the palmar fascia prevents lateral spread, so the infection courses dorsally, resulting in both palmar web space tenderness and dorsal web space swelling and tenderness. The adjacent fingers will be held in abduction with pain on adduction (Fig. 44-19). Incision and drainage, often using separate volar and dorsal incisions, is mandatory, and follows the same treatment as for any abscess or deep-space infection.

Osteomyelitis

Osteomyelitis in the hand usually occurs due to an open fracture with significant soft tissue injury. The presence of infected hardware, peripheral vascular disease, diabetes, and alcohol or drug

abuse are also predisposing factors. Presentation includes persistent or recurrent swelling with pain, erythema, and possible drainage. It will take 2 to 3 weeks for periosteal reaction and osteopenia to be detected on radiographs. Bone scans and MRI are useful modalities to aid in diagnosis. Erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) have low specificity but are useful for monitoring the progress of treatment, with CRP being more reliable. Treatment consists of antibiotics alone in the early stage as long as there is favorable response. All necrotic bone and soft tissue, if present, must be débrided. Initial intravenous antibiotic therapy should cover *S. aureus*, the most common pathogen, and should then be adjusted according to bone cultures. Antibiotic therapy is continued for 4 to 6 weeks once the patient clinically improves and there is no further need for débridement. For osteomyelitis in the setting of an acute fracture with internal fixation in place, the hardware should



A



B

Figure 44-19. A. The fingers surrounding the involved (second) web space rest in greater abduction than the other fingers. B. Dorsal and volar drainage incisions are made, separated by a bridge of intact web skin; a Penrose drain prevents the skin from closing too early.

be left in place as long as it is stable and the fracture has not yet healed. If the hardware is unstable, it must be replaced. An external fixation device may be useful in this setting. If osteomyelitis occurs in a healed fracture, all hardware and necrotic bone and soft tissue must be removed.⁵⁵

Pyogenic Arthritis

Infection of a joint will progress quickly to severe cartilage and bony destruction if not addressed quickly. Direct trauma and local spread of an infection are the most common causes. Hematogenous spread occurs most commonly in patients who are immunocompromised. *S. aureus* is the most common pathogen, followed by *Streptococcus* species. *Neisseria gonorrhoeae* is the most common cause of atraumatic septic arthritis in an adult less than 30 years of age. Presentation includes exacerbation of pain with any joint movement, severe pain on axial load, swelling,

erythema, and tenderness. Radiographs may show a foreign body or fracture, with widened joint space early in the process and decreased joint space late in the process due to destruction. Joint aspiration with cell count, Gram stain, and culture is used to secure the diagnosis. Treatment of nongonococcal septic arthritis includes open arthrotomy, irrigation, débridement, and packing the joint or leaving a drain in place. Intravenous antibiotics are continued until there is clinical improvement, followed by 2 to 4 weeks of additional oral or intravenous antibiotics. Gonococcal septic arthritis is usually treated nonoperatively. Intravenous ceftriaxone is first-line therapy. Joint aspiration may be used to obtain cultures and decrease joint pressure.⁵⁶

Necrotizing Infections

Necrotizing soft tissue infections occur when the immune system is unable to contain an infection, leading to extensive spread with death of all involved tissues. This is different from an abscess, which forms when a functioning immune system is able to “wall off” the infectious focus. Necrotizing infections can result in loss of limb or life, even with prompt medical care.

Bacteria spread along the fascial layer, resulting in the death of soft tissues, which is in part due to the extensive blood vessel thrombosis that occurs. An inciting event is not always identified. Immunocompromised patients and those who abuse drugs or alcohol are at greater risk, with intravenous drug users having the highest increased risk. The infection can be mono- or polymicrobial, with group A β -hemolytic *Streptococcus* being the most common pathogen, followed by α -hemolytic *Streptococcus*, *S. aureus*, and anaerobes. Prompt clinical diagnosis and treatment are the most important factors for salvaging limbs and saving life. Patients will present with pain out of proportion with findings. Appearance of skin may range from normal to erythematous or maroon with edema, induration, and blistering. Crepitus may occur if a gas-forming organism is involved. “Dirty dishwasher fluid” may be encountered as a scant grayish fluid, but often there is little to no discharge. There may be no appreciable leukocytosis. The infection can progress rapidly and can lead to septic shock and disseminated intravascular coagulation. Radiographs may reveal gas formation, but they must not delay emergent débridement once the diagnosis is suspected. Intravenous antibiotics should be started immediately to cover gram-positive, gram-negative, and anaerobic bacteria. Patients will require multiple débridements, and the spread of infection is normally wider than expected based on initial assessment.⁵⁴

Necrotizing myositis, or myonecrosis, is usually caused by *Clostridium perfringens* due to heavily contaminated wounds. Unlike necrotizing fasciitis, muscle is universally involved and found to be necrotic. Treatment includes emergent débridement of all necrotic tissue along with empirical intravenous antibiotics.

Wet gangrene is most common in diabetics with renal failure and an arteriovenous shunt. It is usually polymicrobial. Patients will present with a necrotic digit that is purulent and very malodorous, with rapidly evolving pain, swelling, skin discoloration, and systemic collapse. Emergent treatment is the same as for other necrotizing infections, and amputation of the involved digit or extremity must often be performed.

Infectious Flexor Tenosynovitis

Flexor tenosynovitis (FTS) is a severe pathophysiologic state causing disruption of normal flexor tendon function in the hand. A variety of etiologies are responsible for this process. Most acute cases of FTS are due to purulent infection. FTS also can

occur secondary to chronic inflammation as a result of diabetes, RA, crystalline deposition, overuse syndromes, amyloidosis, psoriatic arthritis, systemic lupus erythematosus, and sarcoidosis.

The primary mechanism of infectious FTS usually is penetrating trauma. Most infections are caused by skin flora, including both *Staphylococcus* and *Streptococcus* species. Bacteria involved vary by etiology of the infection: bite wounds (*Pasteurella multocida*—cat, *E. corrodens*—human); diabetic patients (*Bacteroides*, *Fusobacterium*, *Haemophilus* species, gram-negative organisms); hematogenous spread (*Mycobacterium tuberculosis*, *N. gonorrhoeae*); or water-related punctures (*Vibrio vulnificus*, *Mycobacterium marinum*). Infection in any of the fingers may spread proximally into the wrist, carpal tunnel, and forearm, also known as Parona's space.⁵⁷

Suppurative FTS has the ability to rapidly destroy a finger's functional capacity and is considered a surgical emergency. Suppurative FTS results from bacteria multiplying in the closed space of the flexor tendon sheath and culture-rich synovial fluid medium causing migration of inflammatory cells and subsequent swelling. The inflammatory reaction within the closed tendon sheath quickly erodes the paratenon, leading to adhesions and scarring, as well as increase in pressures within the tendon sheath that may lead to ischemia. The ultimate consequences are tendon necrosis, disruption of the tendon sheath, and digital contracture.

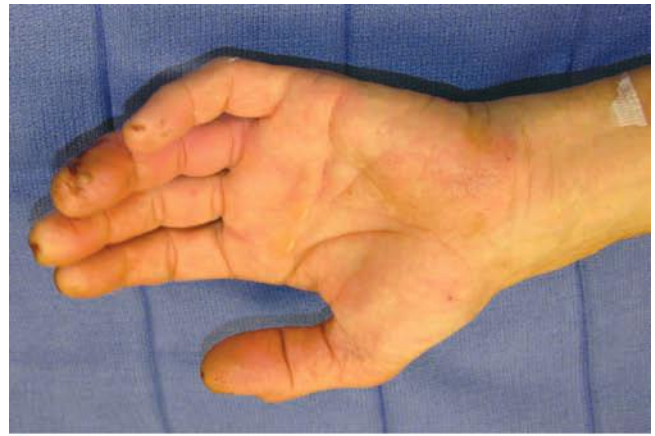
Patients with infectious FTS present with pain, redness, and fever (Fig. 44-20). Physical examination reveals Kanavel's "cardinal" signs of flexor tendon sheath infection: finger held in slight flexion, fusiform swelling, tenderness along the flexor tendon sheath, and pain over the flexor sheath with passive extension of the digit.⁵⁸ Kanavel's signs may be absent in patients who are immunocompromised, have early manifestations of infection, have recently received antibiotics, or have a chronic, indolent infection.

If a patient presents with suspected infectious FTS, empiric intravenous antibiotics should be initiated. Prompt medical therapy in early cases may prevent the need for surgical drainage. For healthy individuals, empiric antibiotic therapy should cover *Staphylococcus* and *Streptococcus*. For immunocompromised patients (including diabetics) or infections associated with bite wounds, empiric treatment should include coverage of gram-negative organisms as well.

Adjuncts to antibiotics include splint immobilization (intrinsic plus position preferred) and elevation until infection is under control. Hand rehabilitation (i.e., range-of-motion exercises and edema control) should be initiated once pain and inflammation are under control.

If medical treatment alone is attempted, then initial inpatient observation is indicated. Surgical intervention is necessary if no obvious improvement has occurred within 12 to 24 hours.

Several surgical approaches can be used to drain infectious FTS. The method used is based on the extent of the infection. Michon developed a classification scheme that can be useful in guiding surgical treatment (Table 44-1).⁵⁹ Figure 44-20B & C demonstrates drainage of a stage II FTS. A Brunner incision allows better initial exposure but may yield difficulties with tendon coverage if skin necrosis occurs. A 16-gauge catheter or 5-French pediatric feeding tube then is inserted into the tendon sheath through the proximal incision. The sheath is copiously irrigated with normal saline. Avoid excessive fluid extravasation into the soft tissue, because the resulting increase in tissue pressure can lead to necrosis of the digit. The catheter is removed after irrigation. The incisions



A



B



C

Figure 44-20. Suppurative flexor tenosynovitis of the ring finger. **A.** The finger demonstrates fusiform swelling and flexed posture. **B.** Proximal exposure for drainage. **C.** Distal drainage incision.

Table 44-1

Michon's stages of suppurative flexor tenosynovitis and appropriate treatment

STAGE	FINDINGS	TREATMENT
I	Increased fluid in sheath, mainly a serous exudate	Catheter irrigation
II	Purulent fluid, granulomatous synovium	Minimal invasive drainage \pm indwelling catheter irrigation
III	Necrosis of the tendon, pulleys, or tendon sheath	Extensive open débridement and possible amputation

are left open. Some surgeons prefer a continuous irrigation technique for a period of 24 to 48 hours. The catheter is sewn in place, and a small drain is placed at the distal incision site. Continuous or intermittent irrigation every 2 to 4 hours with sterile saline can then be performed through the indwelling catheter.

After surgery, an intrinsic plus splint is applied, the hand is elevated, and the appropriate empiric antibiotic coverage is instituted while awaiting culture results. The hand is reexamined the following day. Whirlpool therapy and range of motion are begun. Drains are removed before discharge from the hospital. The wounds are left open to heal by secondary intention. In severe cases, repeat irrigation and operative débridement may be required.

Antibiotic therapy is guided by culture results as well as clinical improvement. Once there is no further need for débridement, a 7- to 14-day course of oral antibiotics is generally prescribed. Consultation with an infectious disease specialist should be considered early in order to maximize efficiency and efficacy of therapy.

Felon

A felon is a subcutaneous abscess of the fingertip and is most commonly caused by penetrating trauma. *S. aureus* is the most common pathogen. The fingertip contains multiple septa connecting the distal phalanx to the skin. These septa are poorly compliant, and presence of an abscess will increase pressure and lead to severe pain and tissue death. Patients will experience erythema, swelling, and tenderness of the volar digital pad. Oral antibiotics may resolve the infection if diagnosed very early, but incision and drainage is indicated when fluctuance is identified. A digital block should be performed, followed by a longitudinal incision over the point of maximal fluctuance (Fig. 44-21). Transverse and lateral incisions should be avoided, and the incision should never extend across the distal phalangeal joint crease. Deep incision should not be performed as this may cause seeding of bacteria into the flexor tendon sheath. The wound is irrigated and packed, with warm soapy water soaks and packing changes initiated within 24 hours and performed two to three times daily until secondarily healed. Antibiotic coverage should cover for *Staphylococcus* and *Streptococcus* species.⁶⁰

Paronychia

Paronychia is an infection beneath the nail fold. The nail plate can be viewed as an invagination into the dorsal skin extending down to the distal phalanx periosteum. Predisposing factors include anything that causes nail trauma, such as manicures,

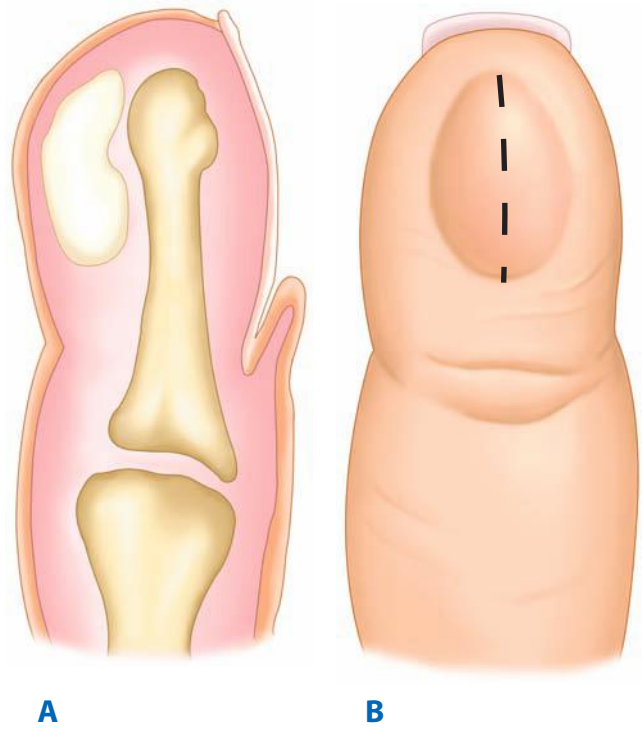


Figure 44-21. Felon. **A.** Lateral view of the digit showing fluctuance between the skin of the pad and the underlying distal phalanx bone. **B.** The authors prefer to drain felons with a longitudinal incision (dashed line) directly over the area of maximal fluctuance.

artificial nails, or nail biting. The infection may spread around the nail plate from one side to the other, or it may extend into the pulp and result in a felon. An acute paronychia is usually caused by *S. aureus* or *Streptococcal* species. Patients report pain, erythema, swelling, and possibly purulent drainage involving the periungual tissue. Treatment consists of warm water soaks and oral antibiotics if diagnosed early. If purulence or fluctuance is present, then a freer elevator or 18-gauge needle can be passed along the involved nail fold to decompress the collection (Fig. 44-22). If the infection involves the eponychial



Figure 44-22. Paronychia. **A.** Fluctuance in the nail fold is the hallmark of this infection. **B.** The authors prefer to drain a paronychia using the bevel of an 18-gauge needle inserted between the nail fold and the nail plate at the location of maximal fluctuance.

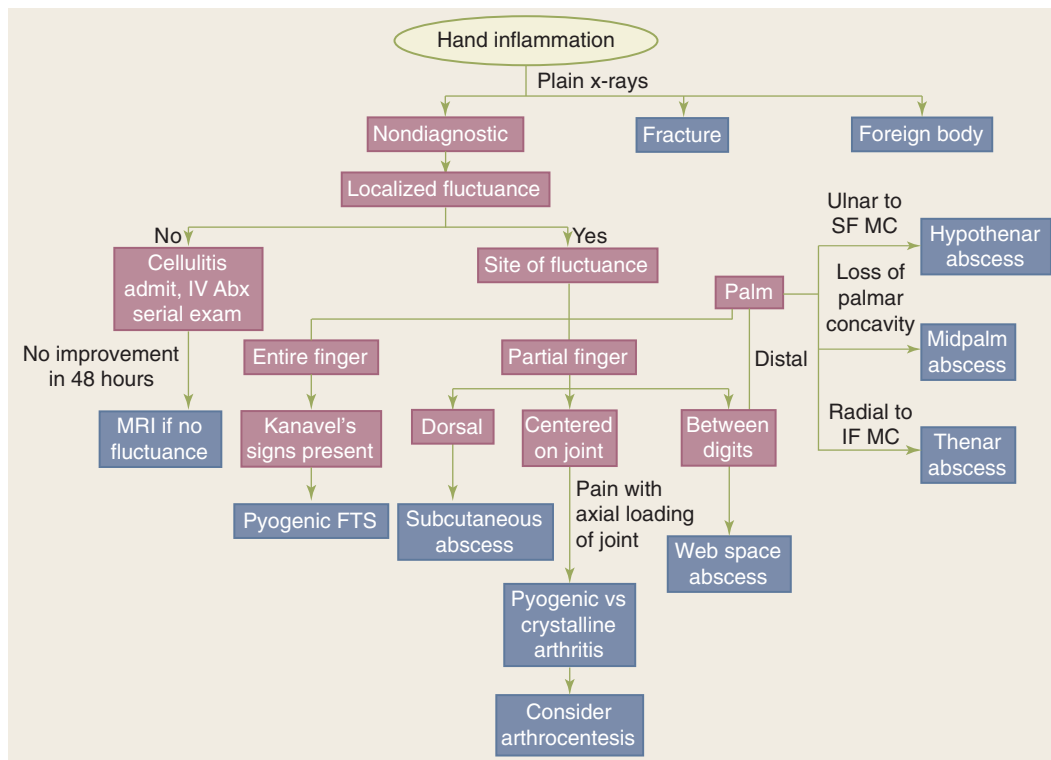


Figure 44-23. Diagnostic algorithm. Diagnostic workup for a patient with hand inflammation to evaluate for infection. See text for details about particular infectious diagnoses. Abx = antibiotics; FTS = flexor tenosynovitis; IF MC = index finger metacarpal; MRI = magnetic resonance imaging; SF MC = small finger metacarpal.

fold, a small proximally based flap of eponychium is created by using a scalpel, followed by irrigation and packing. The nail plate must be removed if the infection extends beneath the nail plate. Packing is kept in place for 24 to 48 hours, followed by warm water soaks and local wound care. Usually, the wound cannot be repacked once the dressing is removed.⁶⁰

A chronic paronychia is most commonly caused by *Candida* species and is most often found in patients who perform jobs involving the submersion of their hands in water or other moist environments. These develop into thickened nails with callus-like formation along the nail folds and may occasionally become red and inflamed. They do not respond to antibiotic treatment, and nail plate removal with marsupialization of the skin proximal to the eponychial fold will allow the wound to heal secondarily. The environmental factors leading to the chronic paronychia must also be corrected in order for treatment to be successful.

All hand infections other than cellulitis will require surgical management. Clinical examination, particularly noting the area of greatest tenderness and/or inflammation, is the single most useful diagnostic tool to localize any purulence requiring drainage. Specific recommendations for differentiating among the possible locations of hand infection are included in the diagnostic algorithm shown in Fig. 44-23.

TUMORS

Tumors of the hand and upper extremity can be classified as benign soft tissue tumors; malignant soft tissue tumors (subclassified into cutaneous and noncutaneous malignancies); benign bony tumors; malignant bony tumors; and secondary metastatic

tumors. Initial investigation for any mass starts with a complete history and physical exam. Hand and/or wrist X-rays should be obtained in every patient presenting with a mass unless clearly not indicated (e.g., a superficial skin lesion with no aggressive/malignant features). The workup proceeds in an orderly fashion until a diagnosis is obtained. Once a benign diagnosis is secured (by strong clinical suspicion in an experienced hand surgeon, radiographic evidence, or tissue biopsy), further workup is not needed; this may occur at any point in the workup of a mass.

Most hand masses are benign and can be readily diagnosed without advanced imaging or tissue biopsy. When necessary, additional workup may include baseline laboratory studies, CT and/or MRI of the involved region, and a bone scan or positron emission tomography (PET) scan. Staging of a malignant tumor may occur before biopsy if a malignancy is strongly suspected, or it may occur after formal biopsy. Staging includes a chest X-ray and CT with intravenous contrast of the chest, abdomen, and pelvis to detect possible metastasis. Biopsy of the mass is always the last step of a workup and should occur only after all other available information has been gathered. Any mass that is over 5 cm in size, is rapidly increasing in size (as judged by an experienced surgeon or oncologist), is symptomatic or painful, or has an aggressive clinical or radiographic appearance warrants workup and biopsy to rule out malignancy.

CT scans are useful for detecting bony tumor extension across planes and identifying tumors of small bones, such as the carpal bones. MRI is useful for evaluating soft tissue tumor involvement (e.g., which muscle compartments are involved) as well as intramedullary lesions. Most soft tissue tumors will appear dark on T1-weighted images and bright on T2-weighted images. Hematomas, hemangiomas, lipomas, liposarcomas,

and adipose tissue will appear bright on T1-weighted images and dark on T2-weighted images. Scintigraphy uses methylene diphosphonate attached to technetium-99m. This complex will attach to hydroxyapatite. Immediate uptake is seen in areas of increased vascularity, such as infection, trauma, and neoplasia. Increased uptake 2 to 3 hours later is seen in “pooled” areas where new bone formation has occurred. This modality is useful for detecting areas of tumor invasion or metastases not otherwise seen on prior CT, MRI, or radiographs.

Biopsy is reserved for masses that cannot be diagnosed as benign based on prior clinical and radiographic exams. Needle biopsy is not reliable for primary diagnosis, but it can be useful for recurrent or metastatic disease. Open excisional (if mass is <5 cm in size) or incisional (if mass is >5 cm in size) biopsy is the most common biopsy method. Proper surgical oncologic technique is strictly adhered to in order to prevent tumor spread into uninvolved tissues or compartments. This includes making all incisions longitudinally using sharp dissection and meticulous hemostasis; carrying the incision directly down to the tumor with no development of tissue planes (i.e., making a straight-line path from skin to tumor); incising through the fewest number of muscle compartments; and avoiding critical neurovascular structures. The CT or MRI images will help determine the best surgical approach for biopsy or resection in order to avoid uninvolved compartments and critical structures.⁶¹

Benign Soft Tissue Tumors

Ganglion Cyst. This is the most common soft tissue tumor of the hand and wrist, comprising 50% to 70% of all soft tissue tumors in this region. They can occur at any age but are most common in the second to fourth decades with a slight predilection toward females. Patients may report a slow-growing soft mass that may fluctuate in size and can sometimes be associated with mild pain. Compressive neuropathies may be seen if they occur in Guyon’s canal or the carpal tunnel, but are uncommon. There are no reports of malignant degeneration.⁶² History and physical exam are usually sufficient to establish a diagnosis. Occurrence by location is as follows: 60% to 70% occur on the dorsal wrist between the third and fourth extensor compartments and are connected by a stalk to the scapholunate ligament (Fig. 44-24); 18% to 20% occur on the volar wrist; and 10% to 12% occur in the digits as volar retinacular or flexor tendon sheath cysts. The cyst transilluminates. There is always a stalk that communicates with the underlying joint or tendon sheath. The cyst wall is composed of compressed collagen fibers with no epithelial or synovial cells present. Clear viscous mucin fills the cyst and is composed of glucosamine, albumin, globulin, and hyaluronic acid. The etiology is unclear. The most accepted theory currently is Angelides’ who proposed that repeated stress of a joint, ligament, or tendon sheath causes an increase of mucin-producing cells and subsequent mucin production. The increased mucin production dissects superficially and coalesces into a cyst. The successful treatment of dorsal ganglion cysts by excising only the stalk supports this theory.⁶³

Treatment consists of observation if asymptomatic. If symptoms exist or the patient desires removal for cosmetic appearance, aspiration of the cyst may be performed with a successful cure rate ranging from 15% to 89%. The benefit of injected steroids is inconclusive. Aspiration of a volar wrist ganglion cyst can be dangerous due to the potential of injuring neurovascular structures. Open excision and arthroscopic excision of the cyst stalk are surgical options for cysts that are not



Figure 44-24. Dorsal wrist ganglion cyst. These typically occur between the third and fourth dorsal extensor compartments and have a stalk connecting the base of the cyst to the scapholunate ligament.

amenable to aspiration. Recurrence rate after surgical excision ranges from 4% to 40%.⁶²

Mucous Cyst. A mucous cyst is a ganglion cyst of the DIP joint. They occur most commonly in the fifth to seventh decades, and the underlying cause is associated osteoarthritis of the DIP joint. They are slow growing and usually occur on one side of the terminal extensor tendon between the DIP joint and the eponychium. The earliest clinical sign is often longitudinal grooving of the involved nail plate followed by a small enlarging mass and then attenuation of overlying skin. X-rays will show signs of osteoarthritis within the DIP joint. Heberden nodes (osteophytes within the DIP joint) are often seen on X-ray.

Possible treatment includes observation, aspiration, or excision. If the cyst is not draining and the overlying skin is intact, the patient may be offered reassurance. A draining cyst poses risk of DIP joint infection due to the tract communicating with the DIP joint and should be excised. If the cyst is symptomatic, painful, or the patient desires removal for cosmetic purposes, excision should be performed. Any osteophytes in the DIP joint must be removed to reduce recurrence. Aspiration is an option for treatment, but this poses the risk of DIP joint infection through seeding of bacteria into the joint or by the development of a draining sinus tract. It is generally not performed.

Giant Cell Tumor of the Tendon Sheath. Also known as a fibrohistiocytoma, fibrous xanthoma, localized nodular

synovitis, or pigmented villonodular synovitis, this is the second most common soft tissue mass of the hand and wrist. It is a benign lesion with no clear pathogenesis. The tumor is a growth of polyclonal cells with no risk of metastases. Despite the similarity in name, it is not histopathologically related to giant cell tumor of the bone.⁶⁴

Giant cell tumor of the tendon sheath occurs as a firm slow-growing painless mass over months to years and will often feel bumpy or nodular, which is a distinguishing characteristic helpful for diagnosis. It has a predilection for occurring in close proximity to joints along flexor surfaces of the wrist, hands, and digits (especially the PIP joints of the radial digits) and occurs most commonly between the second and fifth decades (Fig. 44-25A). These tumors do not transilluminate. Direct extension into joints and ligaments can make complete excision difficult. Gross appearance of the tumor will show a well-circumscribed nodular firm mass with a deep brown color due to the large amount of hemosiderin content, which is easily detected on histologic staining (Fig. 44-25B). Multinucleated giant cells and hemosiderin-laden macrophages are characteristic.⁶⁴

This tumor is not visible on radiographs. Approximately 20% will show extrinsic cortical erosion on X-ray. This is a risk factor for recurrence, and removal of the cortical shell should be considered. MRI is useful for delineating involvement with tendons, ligaments, and joints.

The standard treatment is marginal excision. These tumors will often grow next to or around neurovascular bundles, and an Allen's test should always be performed preoperatively to

confirm adequate blood supply by both ulnar and radial arteries as well as dual blood supply to an involved digit via the ulnar and radial proper digital arteries. It is important to completely excise the stalk because this will greatly reduce tumor recurrence even in the setting of residual tumor. If tumor is suspected to have extended into the joint, the joint must be opened and all tumor removed. Despite this being a benign lesion, local recurrence is approximately 30% (range, 5%–50%). Some variants can mimic more aggressive processes, and malignancy must be considered if aggressive features are identified, such as direct bony invasion.⁶⁴

Lipoma. Lipomas of the hand and wrist may occur in multiple anatomic locations, including subcutaneous tissues; intramuscularly (especially thenar or hypothenar muscles); deep spaces; carpal tunnel or Guyon's canal; and rarely bone or nerve. They typically present as a painless, slow-growing, soft, and mobile mass over a period of months to years. Painful findings suggest close approximation to a neurovascular structure or, less commonly, a malignant lesion such as liposarcoma. Lipomas do not transilluminate. They resemble mature fat histologically. X-rays typically reveal no abnormality. MRI is the most helpful imaging modality to evaluate a lipoma and will show a bright T1 lesion and dark T2 lesion.⁶⁵

Asymptomatic lesions with no aggressive findings may be observed. Marginal excision is recommended for symptomatic, painful, or enlarging lipomas or those that cause dysfunction. MRI is recommended for deep lipomas to evaluate proximity or involvement of critical structures, followed by marginal excision if MRI findings are consistent with a lipoma. If MRI findings are not consistent with a lipoma, incisional biopsy is warranted. Recurrence after marginal excision is rare. Malignant degeneration to liposarcoma is exceedingly rare but has been reported.

Schwannoma. A schwannoma, also known as a neurilemmoma, is a type of benign peripheral nerve sheath tumor. It is the most common benign peripheral nerve sheath tumor of the upper extremity.⁶⁶ The majority occur as single solitary masses. Patients with neurofibromatosis type 1 (NF1) or 2 (NF2) may develop multiple schwannomas involving large peripheral nerve trunks or bilateral acoustic schwannomas, respectively. These tumors arise from the Schwann cell and occur most often in the middle decades of life. They grow as painless, slow-growing, firm, round, well-encapsulated masses with a predilection toward flexor surfaces of the forearm and palm (given their presence of large nerves). Schwannomas grow from the peripheral nerve sheath and are usually connected by a pedicled stalk. The tumor is well demarcated and can be readily separated from the nerve fascicles (Fig. 44-26). Unlike neurofibromas, they do not grow within the nerve. Paresthesias or other neurologic findings may occur, but they are usually absent, as is the Tinel's sign. Findings such as pain, paresthesias, or numbness should raise concern for a tumor causing a compressive neuropathy or a tumor that is malignant.⁶⁶

Histologic exam reveals Antoni type A palisades of spindle cells with large oval nuclei with interlacing fascicles. Less cellular regions appear as Antoni type B areas. Mutations of the schwannomin gene on chromosome 22 are found in 50% of sporadic cases and 100% of acoustic schwannomas in patients with NF2.⁶⁷

Surgical treatment is reserved for symptomatic tumors and those that require biopsy to rule out a malignant process. An MRI should be obtained prior to surgery to confirm that the



A



B

Figure 44-25. Giant cell tumor of tendon sheath. **A.** The mass produces lobulated enlargement of the external finger. **B.** The excised giant cell tumor has a multilobulated, tan-brown appearance.



Figure 44-26. Schwannomas grow as a firm, round, well-encapsulated mass within the epineurium of a peripheral nerve. Schwannomas are able to be separated from the nerve fascicles relatively easily because they do not infiltrate between them (unlike neurofibromas).

tumor is not located within the nerve (i.e., a neurofibroma) and that it is consistent with a schwannoma. Operative treatment involves excisional biopsy. If the tumor is adherent to adjacent soft tissue or not encapsulated, incisional biopsy is performed and excision is delayed pending pathology results. Malignant degeneration is exceedingly rare.⁶⁶

Malignant Soft Tissue Tumors—Cutaneous

Squamous Cell Carcinoma. Squamous cell carcinoma (SCC) is the most common primary malignant tumor of the hand, accounting for 75% to 90% of all malignancies of the hand. Eleven percent of all cutaneous SCC occurs in the hand.⁶⁸ It is the most common malignancy of the nail bed. Risk factors include sun exposure, radiation exposure, chronic ulcers, immunosuppression, xeroderma pigmentosa, and actinic keratosis. Marjolin's ulcers represent malignant degeneration of old burn or traumatic wounds into an SCC and are a more aggressive type. Transplant patients on immunosuppression have a four-fold increased risk and patients with xeroderma pigmentosa have a 1000-fold increased risk of developing an SCC. They often develop as small, firm nodules or plaques with indistinct margins and surface irregularities ranging from smooth to verruciform or ulcerated (Fig. 44-27). They are locally invasive, with 2% to 5% lymph node involvement. Metastasis rates of up to 20% have been reported in radiation or burn wounds. Standard treatment is excision with 0.5- to 1.0-cm margins. Other treatment options include curettage and electrodesiccation, cryotherapy, and radiotherapy.⁶⁸

Basal Cell Carcinoma. Basal cell carcinoma (BCC) is the second most common primary malignancy of the hand, accounting for 3% to 12%; 2% to 3% of all BCCs occur on the hand. Risk factors are similar for SCC and include chronic sun exposure, light complexion, immunosuppression, inorganic arsenic exposure, and Gorlin's syndrome. Presentation includes a small, well-defined nodule with a translucent, pearly border and



Figure 44-27. Squamous cell carcinoma involving the nail fold and nail bed. Note the wart-like and ulcerated appearance.

overlying telangiectasias (Fig. 44-28). Metastasis is very rare. Standard treatment is excision with 5-mm margins. Other treatment options include curettage and electrodesiccation, cryotherapy, and radiotherapy.⁶⁸



Figure 44-28. Basal cell carcinoma of the dorsal hand with surrounding telangiectasia.

Melanoma. Melanoma accounts for approximately 3% of all primary malignant hand tumors.⁶⁹ Risk factors include sun exposure (especially blistering sunburns as a child), dysplastic nevi, light complexion, family history of melanoma, and congenital nevi. Pigmented lesions with irregular borders, color changes, increase in growth, or change in shape are suggestive of melanoma. Breslow thickness is the most important factor in predicting survival for a primary melanoma. Surgical treatment includes excision with 1-cm margins for lesions up to 1 mm in thickness and 2-cm margins for lesions over 1 mm in thickness. Sentinel lymph node biopsy is done for lesions over 1 mm in thickness or for any lesion that is ulcerated and over 0.76 mm in thickness.⁷⁰ Any clinically palpable lymph node requires a formal lymph node dissection of the involved basin, as do sentinel lymph nodes positive for melanoma. Lymph node dissection has not been shown to offer any survival benefit, but the information gained from sentinel lymph node biopsy (or lymph node dissection) does offer valuable staging information that is important for prognosis. Subungual melanomas are treated with DIP amputation, with 5-year survival reported at 66%.⁷¹

Malignant Soft Tissue Tumors—Noncutaneous

Primary soft tissue sarcomas of the upper extremity are very rare, and most hand surgeons will only see several throughout their entire career. Only 14% of all soft tissue sarcomas occur in the entire upper extremity. Statistical inference is limited due to the rare occurrence of these tumors, but mortality rate is very high despite the aggressive treatments. Fewer than 5% of soft tissue sarcomas of the upper extremity will develop lymph node metastasis. Cutaneous malignancies must be considered in the differential diagnosis for any patient with palpable lymph nodes in the setting of any upper extremity mass. Any lesion of the upper extremity that is over 5 cm in diameter, rapidly enlarges, or is painful should be considered malignant until proven otherwise.⁷²

Treatment for soft tissue sarcomas can range from palliative debulking to attempted curative resection. Many muscles of the upper extremity and their compartments cross joints (e.g., forearm flexors). Any malignancy within a compartment mandates complete resection of that compartment, and therefore, amputations must often be performed at levels much more proximal than the level of the actual tumor. Many soft tissue sarcomas are not responsive to radiation or chemotherapy, and use of these adjuvant treatments must be decided upon after discussion with medical and radiation oncologists in a multidisciplinary team. Several studies have shown higher mortality rates in patients who undergo initial tumor biopsy of sarcomas at institutions from which they do not ultimately receive treatment. These studies recommend biopsy be performed at the institution at which definitive treatment will be provided.⁷³ Institutions best suited for such treatment should have pathologists familiar with soft tissue sarcomas, medical and radiation oncologists, surgical oncologists, and a multidisciplinary tumor board.

An in-depth review of each type of soft tissue sarcoma is beyond the scope of this chapter. *Epithelioid sarcoma* is the most common primary soft tissue sarcoma of the upper extremity and usually presents as a benign-like slow-growing mass during the third or fourth decades. It has a propensity for the forearm, palm, and digits. Spread to lymph nodes has been reported. It typically spreads along fascial planes.⁷⁴ *Synovial sarcoma* is argued by some to be the most common primary soft tissue sarcoma of the *hand and wrist*, but the paucity of

case reports is inconclusive. It is a high-grade malignancy that is painless and slow-growing and usually occurs adjacent to, but not involving, joints. It is most common in the second to fifth decades of life. Tumor size (>5 cm) is positively correlated with mortality. Other sarcomas include malignant fibrous histiocytoma, liposarcoma, fibrosarcoma, dermatofibrosarcoma protuberans, and malignant peripheral nerve sheath tumors, and more information can be found in further selected reading.⁷⁵ The majority of metastases to the hand involve secondary bone tumors and are discussed later in the section Secondary Metastatic Tumors.

Benign Bone Tumors

Primary benign bone tumors of the hand and wrist make up a total of 7% of all primary benign bone tumors in the body. Benign tumors of cartilage origin comprise 79% of all primary benign bone tumors of the hand and wrist.⁷⁶

Enchondroma. This is the most common primary benign bone tumor of the hand and wrist and is of cartilage origin. Up to 90% of *all* bone tumors in the hand and wrist are enchondromas, with 35% to 54% of all enchondromas occurring in the hand and wrist. They are often found incidentally on X-rays taken for other reasons (e.g., hand trauma). They are usually solitary and favor the diaphysis of small tubular bones and are most common in the second and third decades of life. The most common location is in the proximal phalanges, followed by the metacarpals and then middle phalanges. Enchondroma has never been reported in the trapezoid. Presentation is usually asymptomatic, but pain may occur if there is a pathologic fracture or impending fracture. The etiology is believed to be from a fragment of cartilage from the central physis. Histology shows well-differentiated hyaline cartilage with lamellar bone and calcification.⁷⁶

Two variants of enchondroma include Ollier's disease (multiple enchondromatosis) and Maffucci's syndrome (multiple enchondromatosis associated with multiple soft tissue hemangiomas). Malignant transformation is very rare in the solitary form, but there is a 25% incidence by age 40 in Ollier's patients and a 100% life-time incidence in Maffucci's patients. When malignant transformation does occur, it is almost uniformly a chondrosarcoma with pain and rapid growth.⁷⁷

Diagnosis is usually made based on history, physical exam, and X-rays. There is a well-defined, multilobulated central lucency in the metaphysis or diaphysis that can expand causing cortical thinning or, sometimes, thickening (Fig. 44-29A). Further imaging is seldom needed, but a CT would be the study of choice.

Observation is indicated for asymptomatic enchondromas with no risk of impending fracture, followed by annual X-rays for 2 years. If a pathologic fracture is found, it is treated with immobilization until fracture union and then surgically treated. If there is any uncertainty as to whether it is an enchondroma, incisional biopsy is indicated and definitive treatment is postponed pending final pathology. Symptomatic lesions and those with impending fracture are treated surgically. Surgical treatment consists of an open incisional biopsy and confirmation by frozen section that it is well-differentiated hyaline cartilage. Curettage and high-speed burring are used to ablate the tumor. Intraoperative fluoroscopy is used to confirm complete ablation (Fig. 44-29B). The defect is then packed with bone graft or bone substitute. Recurrence ranges from 2% to 15%. X-rays should be obtained serially after surgery.⁷⁶

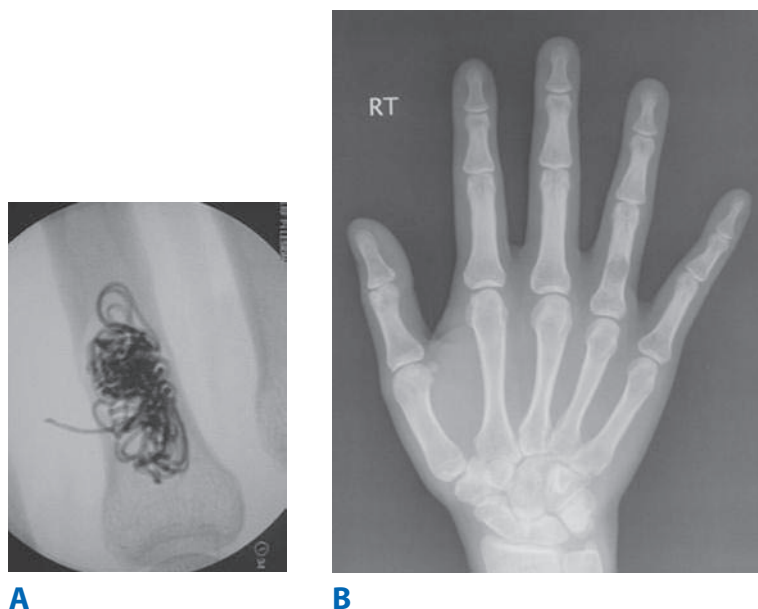


Figure 44-29. Enchondroma. **A.** X-ray of the phalanx demonstrates a well-defined central lucency. Surrounding cortex may thin or thicken. Thinning of the cortex contributes to risk of pathologic fracture. **B.** Intraoperative fluoroscopy after curettage of the tumor. A radiopaque ribbon is used to occupy the defect to help ensure that there is no tumor (similarly radiolucent to the defect after curettage) left behind prior to bone grafting.

Periosteal Chondroma. Periosteal chondromas are benign bone tumors of cartilage origin that arise most commonly within or adjacent to periosteum at the metaphyseal-diaphyseal junction in phalanges. They occur usually in the second or third decade as solitary lesions with pain, swelling, deformity, and possible pathologic fracture. X-rays reveal a subperiosteal lytic, unilobular lesion with erosion into adjacent cortex. There is often a rim of sclerosis. Histologically, they appear as aggressive cartilage with atypia, and it can be difficult to differentiate these from chondrosarcomas.⁷⁶

Diagnosis involves X-rays with incisional biopsy to confirm the benign diagnosis and avoid unnecessary amputation. Treatment includes en-bloc resection of periosteum and corticocancellous bone. Recurrence is less than 4%.

Osteoid Osteoma. This is a tumor of bone origin. Approximately 5% to 15% of all osteoid osteomas occur in the hand and wrist and are most often found in the proximal phalanx or carpus. They usually occur in the second or third decade and present with a deep, dull ache that is classically worse at night and relieved by nonsteroidal anti-inflammatory drugs (NSAIDs). X-rays reveal a central lucency that is usually less than 1 cm in diameter surrounded by reactive sclerosis. Bone scan or CT is helpful to secure the diagnosis.⁷⁸

Treatment consists of NSAID therapy only, and resolution occurs at an average of 33 months. If the patient does not wish to undergo prolonged discomfort with conservative therapy, curettage or percutaneous ablation of the nucleus may be performed.⁷⁸

Giant Cell Tumor of Bone. Giant cell tumors of bone make up only 5% of all benign bone tumors in the body, and only 12% of these occur in the hand or wrist. Although its name is similar to that of “giant cell tumor of tendon sheath,” they are two separate tumors and do not share the same clinical or histopathologic characteristics. Approximately 2% occur in the hand and 10% occur in the distal radius; those within the distal radius are more aggressive. They usually occur in the fourth decade with pain and swelling and possibly pathologic fracture.⁷⁹

Giant cell tumor of the bone is unique in that it is benign on histology but does have metastatic potential and can cause

death. It should be considered a low-grade malignancy.⁷⁹ Workup includes a CT of the chest and total-body scintigraphy to evaluate for metastases and multifocal lesions and MRI to evaluate the extent of local tissue involvement. Treatment consists of amputation of involved phalanges or metacarpals and wide excision of entire carpal rows. Local and systemic surveillance must be done for at least 10 years because metastasis has been reported to occur as late as 10 years postoperatively.⁷⁹

Malignant Bone Tumors

Malignant primary and secondary bone tumors of the hand, like soft tissue malignancies, are exceedingly rare. An in-depth review is beyond the scope of this chapter. The same principles for soft tissue sarcomas of the upper extremity apply here with regard to evaluation, biopsy, and treatment.

Chondrosarcoma comprises 41% of all primary malignant bone tumors of the hand and wrist but only 1.5% of all chondrosarcomas overall. It is most likely to occur from malignant degeneration from a preexisting lesion, with enchondromatosis and osteochondromatosis being the most common. It usually presents as a slow-growing, painless mass in the fourth to sixth decades and can be difficult to differentiate from its benign counterparts. X-ray reveals endosteal erosion, cortical expansion, cortical destruction, and calcification. Metastasis has never been reported for chondrosarcomas of the hand. Chondrosarcomas are not responsive to chemotherapy or radiation.⁸⁰

Osteosarcoma of the hand is exceedingly rare; only 0.18% of osteosarcomas occur in the hand. It usually presents as a painful swelling with pathologic fracture in the fifth to eighth decades of life. Radiation exposure is believed to be a possible risk factor. X-ray findings vary widely, with 90% of tumors occurring at a metaphyseal location. Findings include an osteoblastic or osteolytic lesion, cortical breakthrough with soft tissue extension, a “sunburst” pattern radially, or periosteal elevation (Codman’s triangle). The presence or absence of metastasis is the most important prognostic factor, with a 5-year survival of 70% in the absence of metastases and a 5-year survival of 10% if present. Preoperative chemotherapy is usually given, but radiation therapy plays no role.⁸¹

Secondary Metastatic Tumors

Metastases to the hand or wrist are rare, with only 0.1% of skeletal metastases occurring in the hand. The majority of metastases to the hand are bone lesions, but soft tissue metastases have been reported. The most common primary site is the lung (40%), followed by the kidney (13%) and the breast (11%). Approximately 16% will have no known diagnosis of cancer.⁸² The most common sites are the distal phalanges, followed by the proximal and middle phalanges, metacarpals, and carpus. Patients will present with pain, swelling, and erythema. Differential diagnosis includes felon, gout, osteomyelitis, trauma, RA, or skin cancer. Treatment of a hand or wrist metastatic lesion must not interfere with treatment of the primary cancer. Treatment is usually palliative (simple excision or amputation). The average life expectancy for these patients is less than 6 months.⁸²

BURNS

The palm of the hand makes up only 1% of total body surface area. A burn involving the entire hand and digits is unlikely to cause life-threatening injury or shock, but seemingly small burns to the hand may cause severe permanent loss of function if not treated appropriately. Burns to the hand can cause serious short- and long-term disability. All burns to the hand are considered severe injuries that warrant transfer to a dedicated burn center for specialized treatment. This management will include a multidisciplinary team consisting of hand surgeons, burn surgeons, burn-specialized nurses, occupational therapists, case managers, and social workers.

First-degree burns involve damage to the epidermis only and present with erythema, no blistering, and full sensation with blanching of skin. These will heal without scarring. Second-degree burns are classified as superficial or deep. Superficial second-degree burns involve damage to the papillary dermis; all skin appendages are preserved, and therefore, these readily reepithelialize with minimal to no scarring. Superficial second-degree burns are sensate and present with pain, erythema, blistering, and blanching of skin. Topical dressings are the mainstay of treatment. Deep second-degree burns involve damage to the reticular dermis with damage to skin appendages, as well as the dermal plexus blood vessels and nerves. These have decreased sensation and no cap refill and appear pale or white. Blistering may be present. Damage to the skin appendages and blood supply in the dermal plexus precludes spontaneous healing without scar. Excision with skin grafting is needed. Third-degree burns involve full-thickness damage through the dermis and are insensate with no blistering. They appear dry, leathery, and even charred.

Acute Management

Advanced Trauma Life Support guidelines should be followed. After primary survey, circulation to the hand should be assessed. Palpation and Doppler ultrasound should be used to evaluate blood flow within the radial and ulnar arteries, the palmar arches, and digital blood flow at the radial and ulnar aspect of each volar digital pad. A sensorimotor exam should be performed. Objective evidence of inadequate perfusion (i.e., deteriorating clinical exam with changes in or loss of pulse or Doppler signal) indicates the need for escharotomy, especially in the setting of circumferential burns. Escharotomy may be performed at bedside with scalpel or electrocautery under local anesthesia or intravenous sedation. The depth

of the escharotomy incision should extend into the dermis but not into subcutaneous tissues. In the forearm, axially oriented midradial and midulnar incisions are made for the entire extent of the burn. Escharotomy should proceed as distally as necessary into the wrist and hand to restore perfusion. Digital escharotomies are made via a midaxial (the middle of the longitudinal axis on sagittal view) incision over the radial aspects of the thumb and small finger and the ulnar aspects of the index, middle, and ring fingers.⁸³ These locations for digital escharotomies avoid painful scars on the heavy-contact surfaces of each respective digit. After primary survey, vascular, and sensorimotor exams are complete, careful documentation should be made of all burns. This is best done with a Lund and Browder chart and includes location, surface area, and initial depth of burn.

The burns should be dressed as soon as examination is complete. Gauze moistened with normal saline is a good initial dressing because it is easy, readily available, and will not leave ointment or cream on the wounds, which can hinder frequent examinations in the initial period. It is critical that no dressing is wrapped in a circumferential manner around any body part. Edema and swelling can lead to extremity ischemia if a circumferential dressing is in place. It is important to maintain body temperature above 37°C, especially in burn patients who have lost thermoregulatory function of the skin and now have moist dressings in place. The hands should be elevated above heart level to decrease edema formation, which can hinder motion and lead to late scar contracture. The hand should be splinted in the intrinsic plus position with the MPs flexed to 90° (placing MP collateral ligaments under tension), the IPs in straight extension (prevents volar plate adhesion), and the wrist in approximately 15° of extension.⁸⁴ If the burn involves the thenar eminence, thumb, or first web space, the thumb should be splinted in full abduction (to open up the first web space). Any other web space that is burned should have the adjacent fingers splinted in abduction. This will help prevent web space contracture. In rare cases, Kirschner wires or heavy steel wires/pins are needed to keep a joint in proper position. These are placed percutaneously through the involved joint and serve as a temporary joint stabilizer.

After the primary and secondary surveys are complete, the wound should be evaluated again. Devitalized tissue should be débrided. Wounds should be cleansed twice daily, typically with normal saline. Second-degree superficial burns may be dressed with Xeroform gauze and Bacitracin. Silver sulfadiazine cream is another option for any second- or third-degree wound. It covers gram-positive and gram-negative microbes, but it does not penetrate eschar. It should be applied at least one-sixteenth of an inch thick. Sulfamylon can be used in conjunction with silver sulfadiazine or alone. It deeply penetrates eschar and tissues and has good gram-positive coverage.

After débridement of necrotic skin, grafting will eventually be necessary. Allograft (human cadaver skin) is an expensive but useful temporary dressing for second- and third-degree burns. It can remain in place for up to 14 days before the body will reject it. It typically is left in place for 7 days. Allograft stimulates a wound to begin healing and can also serve as a way of “testing” a wound that needs skin grafting. If the allograft is adherent and there is evidence of temporary ingrowth, this suggests that the wound is ready to receive a skin graft.

Occupational hand therapy has played a major role in preserving hand function following burn injuries. Reestablishment

of hand function is pivotal for burn patients and is directly dependent on their ability or effort to participate with an occupational therapist. Early work with an occupational therapist can minimize the need for later reconstruction.⁸⁴ Hand therapy should be initiated as soon as possible. Hand therapists are also able to make customized molded splints that facilitate frequent dressing changes.

Surgical Management

Any burn wound will eventually heal with proper wound care. However, this may involve unacceptable scarring, deformity, contractures, pain, and unstable wounds that are prone to breakdown. The goal is to restore preinjury function as much as possible with a wound that is durable, supple, nonpainful, and allows the patient to return to society as an active member. Local wound care is the ideal treatment for wounds that can heal completely within 14 days while not sacrificing function. Purely cosmetic concerns are addressed after complete scar maturation (~12 months). In other cases, surgical excision and skin grafting are necessary. Skin grafting should be done as soon as it becomes obvious that a wound will not be healed completely by postburn day 14. It should also be considered for wounds that are likely to cause contractures, especially along the joints and web spaces.⁸⁴

Considerable controversy surrounds the need, timing, and method of grafting burns. Careful consideration must be given to the patient's overall status, their preinjury state, and the type of work and recreational activities they enjoyed in order to have a better understanding of which issues should be addressed.⁸⁵ Tangential excision of the wounds should be performed under tourniquet to minimize blood loss and is carried down to viable tissue. Avoid excising through fascia (epimysium) overlying muscles or exposing tendons, bone, joint capsules, or neurovascular structures. Tissues capable of receiving a skin graft include well-vascularized fat, muscle, perineurium, paratenon, perichondrium, and periosteum. Exposure of deep structures without an adequately graftable bed mandates further coverage before skin grafting can occur (discussed later in Reconstruction section).

Once there is an adequate bed, grafting is the next step. If there is any doubt as to whether the wound bed can support a skin graft, a temporary dressing should be placed and the patient reexamined frequently for signs of granulation tissue and wound bed viability. Skin grafts to the dorsum of the hand are typically split-thickness sheet grafts (not meshed). There are no functional differences between a sheet graft and a meshed graft, but sheet grafts have a much better final appearance. Skin grafts to the palmar aspects of the hand should be full-thickness in order to provide the dermal durability needed for daily functions.⁸⁴ Skin grafts are secured with staples, sutures, fibrin glue, or even skin glue. It is important to bolster every skin graft. This prevents shearing loss and also keeps the skin graft in contact with the wound bed, preventing fluid collections that can lead to graft loss. A bolster may consist of a tie-over bolster and a splint or a negative-pressure dressing. The hand should be splinted in intrinsic plus for 7 days after skin grafting. Once the graft is adherent, hand therapy should begin, consisting of active and passive range-of-motion exercises and modalities.

Reconstruction

Reconstruction of burn wounds can begin as early as the acute setting and continue into the subacute and late stages. Burns

may initially be superficial but later convert to deep burns (especially with grease, oil, and alkali burns) due to infection, tissue desiccation, or continued trauma, or they may be deep from the outset of injury. Débridement or excision of burns may result in exposure of viable muscle, bone, tendon, cartilage, joints, and neurovascular structures, as well as loss of fascial layers that are required for overlying soft tissue to glide during movement. Simply skin grafting these exposed structures will result in unstable wounds that are prone to chronic breakdown. Soft tissue contractures will develop as the skin grafts adhere to the structures, effectively anchoring them in static position. This is especially true for tendons, where gliding capability is paramount for function. Flap coverage is required in these situations. The reversed radial forearm flap is a local flap and is often the first choice for flap coverage of the hand. If the zone of injury or size of defect precludes its use, other skin and fat flaps, including the free lateral arm, free anterolateral thigh, or even free parascapular flaps, may be useful, provided the patient can tolerate a free tissue transfer (see Chapter 45) operation (Fig. 44-30). The digits may also be buried subcutaneously in the lower abdominal skin or groin crease. Vascular ingrowth from the digits into the abdominal or groin skin occurs over 2 to 3 weeks, allowing division of the flap(s) and achieving full-thickness coverage of the wounds.^{84,85}

An acellular dermal regenerative substitute (e.g., Integra) may be used for wounds that have exposed structures and require more durability than is offered by a skin graft⁸⁶ such as full-thickness loss overlying the extensor tendons of the wrist and hand. Dermal substitute is a good option for wounds that are not extensive enough to warrant a flap and for patients who are poor candidates for an extensive surgery. Integra is composed of acellular cross-linked bovine tendon collagen and glycosaminoglycan with an overlying silicone sheet. It is applied much like a skin graft. After incorporation in 14 to 21 days, it is capable of accepting a skin graft (after removing the silicone sheet). Conceptually, it works by replacing the lost dermis and adds durability to a wound bed. It may be reapplied multiple times to the same area if thicker neodermis is desired. Although cultured autologous keratinocytes have been used, they are expensive, time-consuming, and do not provide prompt or durable coverage. They are not widely used.

Web space contractures are the most common deformity resulting after hand burns. They may occur late despite the best



Figure 44-30. Free anterolateral thigh flap reconstruction of a large dorsal hand wound. Once wound coverage is stable, this flap will need to be surgically revised to achieve proper contour.



A



B

Figure 44-31. Z-plasty release of web space contracture. **A.** First web space burn contracture. **B.** Immediate postoperative result.

efforts. In the normal web space, the leading edge of the volar aspect of the web is distal to the dorsal aspect. This is reversed in web space contractures and limits digit abduction. Local modified Z-plasty (double-opposing Z-plasty) is the preferred treatment (Fig. 44-31).

Special Considerations

Chemical burns pose a risk to healthcare providers and should be considered hazardous material. They must also be removed from the patient or continued burn injury will occur. A complete discussion of all chemicals causing burns is beyond the scope of this chapter. Hydrofluoric acid produces a slow onset of severe pain and continues to penetrate deeper structures. It avidly binds tissue and circulating calcium and can lead to hypocalcemia and cardiac arrest. The wound should be irrigated

copiously with water followed by topical application of an aqueous mixture of calcium gluconate. Calcium gluconate may also be infiltrated intradermally throughout the wound. Effectiveness of treatment is assessed by relief of pain. Intra-arterial injection of calcium gluconate into the artery supplying blood flow is another alternative if the other measures fail.⁸⁷ Alkaline and acid burns require copious irrigation with water, with alkali burns often requiring hours of irrigation. Phenol burns should be irrigated with water and treated topically with polyethylene glycol. Phosphorus burns leave phosphorus particles within the wound. A 0.5% copper sulfate solution is applied to stain the particles black, followed by débridement.^{84,85}

VASCULAR DISEASE

Vascular disease encompasses a broad spectrum of disorders leading to compromised perfusion to the hand and digits and may potentially cause ischemia and necrosis. Chronic vascular disorders tend to develop slowly and are typically seen in older patients. This includes progressive thrombosis, aneurysms, systemic vasculopathy, and vasospastic disorders. Disorders unique or common to the hand are discussed in the following sections.

Progressive Thrombotic Disease

Hypothenar hammer syndrome involves occlusion of the ulnar artery at the wrist and is the most common occlusive vascular disorder of the upper extremity. The etiology is believed to be chronic trauma to the ulnar artery as it exits Guyon's canal. The classic example is a construction worker who frequently uses heavy equipment, such as jackhammers, that cause prolonged vibration and repetitive impact on the ulnar aspect of the palm. This causes periadventitial arterial damage that results in scarring and eventual compression, as well as medial and intimal damage.⁸⁸ The artery then becomes weakened and prone to aneurysm and/or thrombosis. If a thrombus forms, it may embolize, producing digital ischemia. Symptoms may be chronic or acute and include pain, numbness and tingling, weakness of grip, discoloration of the fingers, and even gangrene or ulcers of the fingertips.

If acute in onset, proximal occlusions may be extracted with a balloon catheter or, sometimes, under direct vision via an arteriotomy. Very distal embolism may require infusion of thrombolytics to dissolve clots and allow reperfusion. Large-vessel acute embolism and reperfusion may result in edema and compartment syndrome, requiring fasciotomy. A high index of suspicion must be maintained.

For the more common scenario of chronic, progressive occlusion, the involved segment of ulnar artery should be resected. There is disagreement in the literature regarding whether simple ligation and excision is sufficient for patients with sufficient distal flow or if all patients should undergo vascular reconstruction.⁸⁹ The authors' personal preference is to reconstruct all patients.

Systemic Vasculopathy

Buerger's disease (thromboangiitis obliterans) is an inflammatory occlusive disease affecting small and medium-sized arteries and veins. It is strongly influenced by smoking and will often resolve upon smoking cessation. Typical onset is before 50 years of age. Migratory phlebitis occurs distal to the elbow, resulting in ischemia, ulceration, and necrosis of the digits. It can continue to cause more proximal ischemia and ultimately lead to loss of the hands. Treatment must start with smoking

cessation. Failure to stop smoking will make any surgical intervention unsuccessful. Arteriography is useful to determine arterial flow and whether bypass is possible. If direct bypass is not possible, alternatives include arterialization of the venous system by connecting the dorsal venous network to the brachial artery or possible free microvascular omental transfer beneath the dorsal forearm or hand for indirect revascularization.⁹⁰

Vasospastic Disorders

Raynaud's syndrome results from excessive sympathetic nervous system stimulation. Perfusion is diminished and fingers often become cyanotic. Although the onset of the symptoms is benign, chronic episodes can result in atrophic changes and painful ulceration or gangrene of the digits. Raynaud's disease occurs without another associated disease. This disease predominately affects young women and is often bilateral. The vascular system is structurally intact without any obstructions. There is no ulceration, gangrene, or digit loss. In contrast, Raynaud's phenomenon is associated with an underlying connective tissue disorder, such as scleroderma. Arterial stenosis is present due to disease changes in blood vessels as a result of the specific medical disorder.⁹⁰

Scleroderma is an autoimmune connective tissue disorder resulting in fibrosis and abnormal collagen deposition in tissue. Many organs can be affected, with the skin most commonly and noticeably involved. In this disease, blood vessels are injured by intimal fibrosis leading to microvascular disease. The vessels become subject to Raynaud's phenomenon, and patients develop painful, ulcerated, and sometimes necrotic digits.^{91,92}

Sympathectomy can provide pain relief and healing of ulcers for patients with scleroderma and Raynaud's phenomenon. In this procedure, adventitia is stripped from the radial artery, ulnar artery, superficial palmar arch, and digital arteries in various combinations based on the affected digits being treated. The decrease in sympathetic tone allows for vasodilation and increased blood flow. If the patient notes significant distal pain relief and/or previously ischemic tissue improves in color after a test administration of local anesthetic, sympathectomy may provide the same results in a long-term fashion.^{91,92}

CONGENITAL DIFFERENCES

Congenital differences in a newborn can be particularly disabling as the child learns to interact with the environment by using the hands. The degree of anomaly can range from minor, such as a digital disproportion, to severe, such as total absence of a forearm bone. In recent years, increasing knowledge of the molecular basis of embryonic limb development has significantly enhanced the understanding of congenital differences. Congenital hand differences have an incidence of 1:1500 births. The two most common differences encountered are syndactyly and polydactyly.⁹³

There are numerous classification systems for hand differences. The Swanson classification, adopted by the American Society for Surgery of the Hand, delineates seven groups organized based on anatomic parts affected by types of embryonic failures.⁹⁴

Failure of Formation

The failure of the formation of parts is a group of congenital differences that forms as a result of a transverse or longitudinal arrest of development. Conditions in this group include radial club hand, a deformity that involves some or all of the tissues

on the radial side of the forearm and hand, and ulnar club hand, which involves underdevelopment or absence of the ulnar-sided bones.

Failure of Differentiation

The failure of the differentiation of parts comprises conditions where the tissues of the hand fail to separate during embryogenesis. Syndactyly, in which two or more fingers are fused together, is the most common congenital hand deformity and occurs in seven out of every 10,000 live births. There is a familial tendency to develop this deformity. This deformity often involves both hands, and males are more often affected than females. Syndactyly is classified as either simple (soft tissue only) or complex (bone and/or cartilage also involved), and complete (full length of the digits) or incomplete (less than the full length).

Surgical release of syndactyly requires the use of local flaps to create a floor for the interdigital web space and to partially surface the adjacent sides of the separated digits (Fig. 44-32). Residual defects along the sides of the separated fingers are covered with full-thickness skin grafts. Surgery usually is performed at 6 to 12 months of age.

Duplication

Duplication of digits is also known as polydactyly. Radial polydactyly is usually manifests as thumb duplication. Wassel described a classification system for thumb duplications based on the level of bifurcation.⁹⁵ When two thumbs are present in the same hand, they are rarely both normal in size, alignment, and mobility. In the most common form of thumb duplication, a single broad metacarpal supports two proximal phalanges, each of which supports a distal phalanx. Optimal reconstruction requires merging of elements of both component digits. Usually the ulnar thumb is maintained. If the duplication occurs at the MP joint, the radial collateral ligament is preserved with the metacarpal and attached to the proximal phalanx of the retained ulnar thumb. Surgery is usually performed at 6 to 12 months of age. Ulnar-sided polydactyly may often be treated by simple excision of the extra digit.

Overgrowth

Overgrowth of digits also is known as macrodactyly, which causes an abnormally large digit. In this situation, the hand and the forearm also may be involved. In this rare condition, all parts of a digit are affected; however, in most cases, only one digit is involved, and it is usually the index finger. This condition is more commonly seen in males. Surgical treatment of this condition is complex, and the outcomes may be less than desirable. Sometimes, amputation of the enlarged digit provides the best functional result.

Undergrowth

Underdeveloped fingers or thumbs are associated with many congenital hand deformities. Surgical treatment is not always required to correct these deformities. Underdeveloped fingers may include the following: small digits (brachydactyly), missing muscles, underdeveloped or missing bones, or absence of a digit.

Constriction Band Syndrome

Constriction band syndrome is a set of congenital differences that occurs when a tissue band forms around the digit(s) or arm in utero, impairing blood flow and growth. This condition may

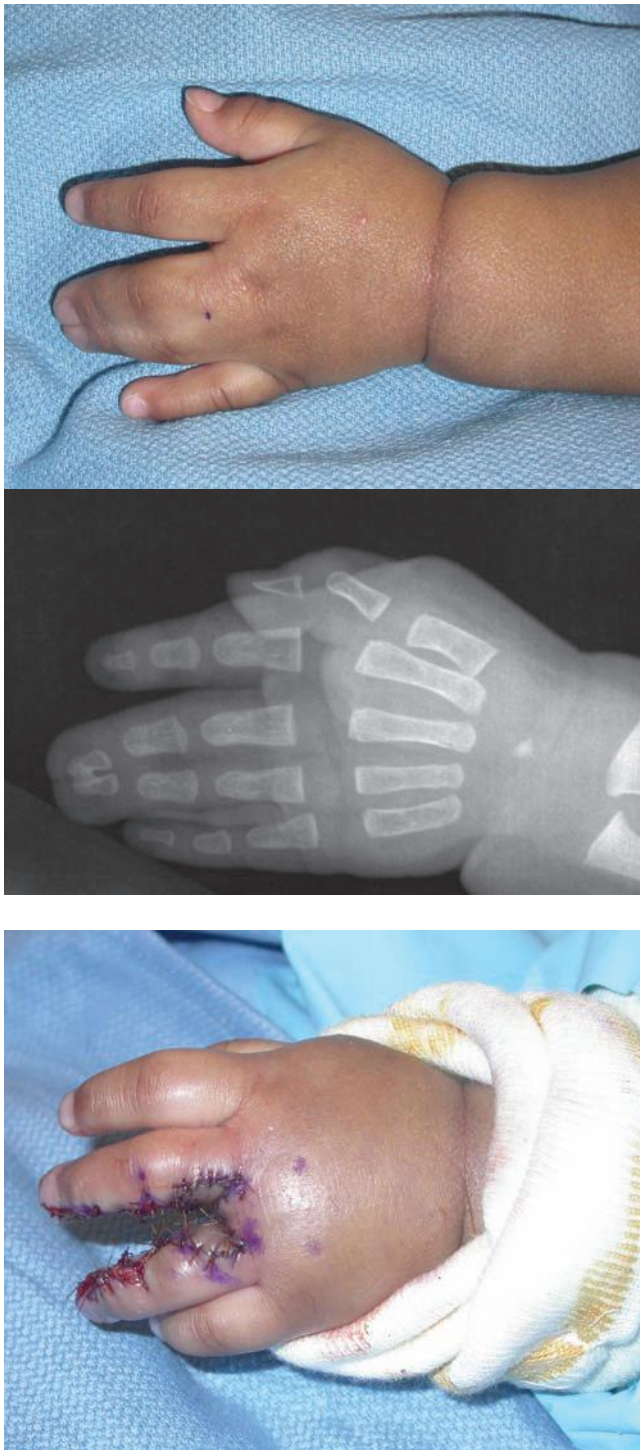


Figure 44-32. Syndactyly. Hand of a 1-year-old patient with complex syndactyly between the long and ring fingers. Complex syndactyly refers to fingers joined by bone or cartilaginous union, usually in a side-to-side fashion at the distal phalanges. The syndactyly is divided with interdigitating full-thickness flaps, a dorsal trapezoidal-shaped flap to resurface the floor of the web space, and full-thickness skin grafts. Note the skin grafts on the ulnar and radial sides of the new web space.

be associated with other problems such as clubfoot, cleft lip, cleft palate, or other craniofacial anomalies. The cause of the ring constrictions is unknown. Some theories suggest that folds or bands in the amniotic membrane may be responsible for this condition.

Generalized Skeletal Anomalies and Syndromes

This is a rare and complex group of unclassified problems.

RECONSTRUCTIVE TRANSPLANTATION OF THE UPPER EXTREMITY

Hand transplantation was first performed in humans in the late 1990s both in Louisville, Kentucky, and Lyon, France.⁹⁶ The treating surgeons were able to successfully remove an upper extremity from a brain-dead donor, attach it to an upper extremity amputee, and have the tissue survive. In the subsequent 15 years, many additional centers have achieved technical success with upper extremity transplantation as well.

The technical considerations of hand transplantation have proven to be only the beginning of challenges in bringing this treatment option to the general public. Replantation of an amputated limb was first reported by Malt in 1962.⁹⁷ In a limb replantation, there is a zone of injury, and cold preservation of the amputated part does not begin immediately. In a limb transplant, the harvest can be done as proximally as necessary to ensure that only healthy tissue is present on both sides of the repair and to obviate the need for limb shortening, and cold preservation of the amputated part can begin immediately after harvest.

A major concern regarding the use of limb transplantation is the immunosuppression medications required to prevent rejection of the transplanted limb. Unlike organ transplantation, which provides a critical organ without which the recipient could not survive or would require chronic mechanical support (e.g., hemodialysis), the absence of one or even multiple limbs does not represent an immediate threat to a patient's survival. Multiple studies have documented the nephrotoxic and other side effects of tacrolimus (FK 506), the principle antirejection agent used in transplant immunomodulation protocols.^{98,99}

Due to these concerns, much research has been directed at minimizing the amount of antirejection medication as well as promoting tolerance or even chimerism. Donor bone marrow transplantation to the limb transplant recipient has been shown to be beneficial toward this purpose and is part of the limb transplant protocol in some centers.¹⁰⁰ Recent research with donor bone marrow infusions has shown that lower levels of immunosuppressive drugs may be possible, as well as fewer immunosuppressive agents.¹⁰⁰ Further research is needed in order to determine the efficacy and utility of donor bone marrow transfusions and how they impact transplant recipients in the short and long term.

The final challenge in consideration of a patient for limb transplantation is selection of an appropriate candidate. There are multiple patient factors that need to be considered to determine if a patient is an appropriate candidate for hand transplantation. These include medical concerns, such as immunologic issues (both antibodies and the presence of occult neoplasms or indolent viruses such as cytomegalovirus), hematologic issues including coagulopathies, and anatomic issues such as quality of skin envelope and amputation level of the bone and neuromuscular structures. Psychological and social factors must also be considered related to the recipient's ability to comply with postoperative medication and therapy protocols as well as to cope with a continuous visible presence of a limb originating from another person.¹⁰¹

The promise of upper limb transplantation as a reconstructive technique remains high. Both civilian and military amputees

stand to receive a marked functional benefit from this treatment. With the number of transplants performed worldwide approaching 100 as well as decades of animal research, understanding of how best to use this technique from functional, patient safety, and cost-effectiveness standpoints continues to grow.

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45 chapter

Plastic and Reconstructive Surgery

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Christopher G. Wallace, and Fu-Chan Wei

Historical Background	1829	Reconstructive Surgery	1852	Pressure Sore Treatment / 1880
General Principles	1829	Facial Reconstruction after Fracture / 1852		Reconstructive Transplant Surgery / 1881
Skin Incisions / 1829		Ear Reconstruction / 1855		Aesthetic Surgery
Wound Healing / 1830		Nasal Reconstruction / 1856		1882
Skin Grafts and Skin Substitutes / 1832		Lip Reconstruction / 1856		Assessment of Facial Aesthetics / 1882
Flaps / 1833		Eyelid Reconstruction / 1858		Blepharoplasty and Browlift / 1882
Free Tissue Transfer / 1838		Skull and Scalp Reconstruction / 1860		Facelift / 1883
Tissue Expansion / 1840		Head and Neck Reconstruction / 1860		Rhinoplasty / 1883
Pediatric Plastic Surgery	1840	Facial Reanimation / 1865		Suction Lipectomy / 1883
Cleft Lip and Palate / 1840		Breast Reconstruction / 1866		Autologous Fat Grafting / 1885
Craniofacial Anomalies / 1844		Trunk and Abdominal Reconstruction / 1872		Excisional Body Contouring / 1886
Vascular Anomalies / 1849		Extremity Reconstruction / 1876		Reduction Mammoplasty / 1887
Congenital Melanocytic Nevi / 1852				Mastopexy / 1889
				Augmentation Mammoplasty / 1890
				Gynecomastia / 1891

HISTORICAL BACKGROUND

The field of plastic surgery focuses on the restoration of form and function to those who have congenital and acquired deformities. Plastic surgery routinely addresses novel problems and challenges; therefore, the plastic surgeon must have an expert knowledge of anatomy and surgical technique to address new challenges.

The word *plastic* is derived from the Greek *plastikos*, meaning “to mold.” Although the term *plastic surgery* can be found in several medical writings from the eighteenth and nineteenth centuries, it was John Staige Davis who established the name of the specialty with the 1919 publication *Plastic Surgery—Its Principles and Practice*.

One of the earliest accounts of reconstructive surgery can be found in the *Sushruta Samhita*, an early text from the sixth or seventh century B.C. by the practitioner Sushruta. In this writing, the reconstruction of an amputated nose with a pedicled forehead flap and the reconstruction of the ear with cheek flaps were described. In addition, in the first century A.D., the Roman physicians Aulus Cornelius Celsus and Paulus Aegineta described operations for facial reconstruction.

The first textbook of plastic surgery is believed to be Gaspara Tagliacozzi’s 1597 publication *De Curtorum Chirurgia per Insitionem*. This text describes the reconstruction of the nose with a pedicled arm flap. The nineteenth century saw advances in reconstructive surgery, including Giuseppe Baronio’s successful grafting of sheepskin. The techniques for perfecting human skin grafting followed later in the nineteenth century.

Great advances in plastic surgery occurred as a result of the first and second world wars. Out of the fields of dental surgery, otolaryngology, ophthalmology, and general surgery, the discipline of plastic surgery was established. The founders of the field include Sir Harold Gillies, an otolaryngologist who established a center for the treatment of maxillofacial injuries in England; V. H. Kazanjian, a dental surgeon from Boston, who established a center in France for the treatment of facial injuries incurred in World War II; and Vilray P. Blair, from St. Louis, who established centers for the treatment of soft tissue and maxillofacial reconstruction for the U.S. Army. With the onset of World War II, centers of excellence for hand reconstruction appeared as well.

In the last 50 years, advances in plastic surgery have included the transplantation of both autologous and allogeneic tissue, tissue expansion, regional muscle and myocutaneous flap transfers, distant transfer of free flaps using microsurgery, replantation of traumatically amputated extremities and digits, and the emergence of craniofacial surgery. The future of plastic surgery will likely see further advances in the realms of regenerative medicine, fetal surgery, and reconstructive transplantation.

GENERAL PRINCIPLES

Skin Incisions

Human skin exists in a state of tension created by internal and external factors. Externally, skin and underlying subcutaneous tissue are acted on by gravity and clothing. Internally, skin is subjected to forces generated by underlying muscles, joint

Key Points

- 1▶ Plastic surgery is the field of surgery that addresses congenital and acquired defects, striving to return form and function.
- 2▶ Plastic surgery has been a field of innovation. The future of the specialty likely includes advancements in the areas of regenerative medicine, fetal surgery, and reconstructive transplantation with composite tissue allotransplants.
- 3▶ Children diagnosed with cleft and craniofacial anomalies benefit from interdisciplinary care at a specialized center focusing on team care. Long-term follow-up during growth and development is critical for optimal outcomes.
- 4▶ Reconstructive surgery attempts to restore form and function through techniques that include skin grafting, use of muscle flaps, bone grafting, tissue expansion, free tissue transfer with microsurgery, and replantation.
- 5▶ Aesthetic surgery is surgery performed to reshape the normal structure of the body to improve the patient's appearance and self-esteem. Patients undergoing aesthetic surgery present a unique challenge. The most important outcome parameter is patient satisfaction, and therefore, a thorough understanding of the patient's motivations, goals, and expectations is critical.

extension and flexion, and tethering of fibrous tissues from zones of adherence. As a result, when skin is incised linearly, it gapes to variable degrees. When a circular skin excision is performed, the skin defect assumes an elliptical configuration paralleling the lines of greatest tension. Carl Langer, an anatomist from Vienna, first fully described these tension lines in the mid-1800s based on his studies of fresh cadavers.¹ A. F. Borges described another set of skin lines that, different from Langer's lines, reflect the vectors of relaxed skin tension.² Although the term *Langer's lines* often is used interchangeably with the term *relaxed skin tension lines*, the former lines describe skin tension vectors observed in the stretched integument of cadavers exhibiting rigor mortis, whereas the latter lines lay perpendicular to and more accurately reflect the action of underlying muscle² (Fig. 45-1). Relaxed skin tension lines may be exploited to create incisions that minimize anatomic distortion and improve cosmesis. In areas of anatomic mobility, such as the neck or over joints, incisions are oriented less for aesthetic reasons and more with the goal of avoiding scar contractures and subsequent functional compromise. In general, incisions are placed perpendicular to the action of the joint.

There are situations, however, in which the direction of the incision has been preestablished, as in acute lacerations, burns,

or old contracted and distorting scars. In these circumstances, the principles of proper incision placement can be combined with simple surgical techniques to reorient the scar and lessen the deformity. The Z-plasty technique uses the transposition of random skin flaps both to break up a linear scar and to release a scar contracture through lengthening (Fig. 45-2; Table 45-1). W-plasty is the technique of scar excision and reconstruction in zigzag fashion to camouflage the resulting scar.

Wound Healing

The fundamentals of plastic surgery are based on wound healing physiology. Wound repair consists of an exquisitely regulated symphony of molecular and cellular instruments that act in concert to restore the local tissue environment to prewound conditions. Metabolic imbalances in the wound milieu drive this orchestration and continue to direct it until healing resolves the disturbance. Although a detailed review of wound physiology is presented elsewhere in this text, it is useful to emphasize several points.

Tissue injury disrupts the tissue microenvironment and sets into motion a cascade of events that combine to reestablish the environmental status quo. Disrupted blood vessels fill the wound space with red blood cells and plasma. Injured cells



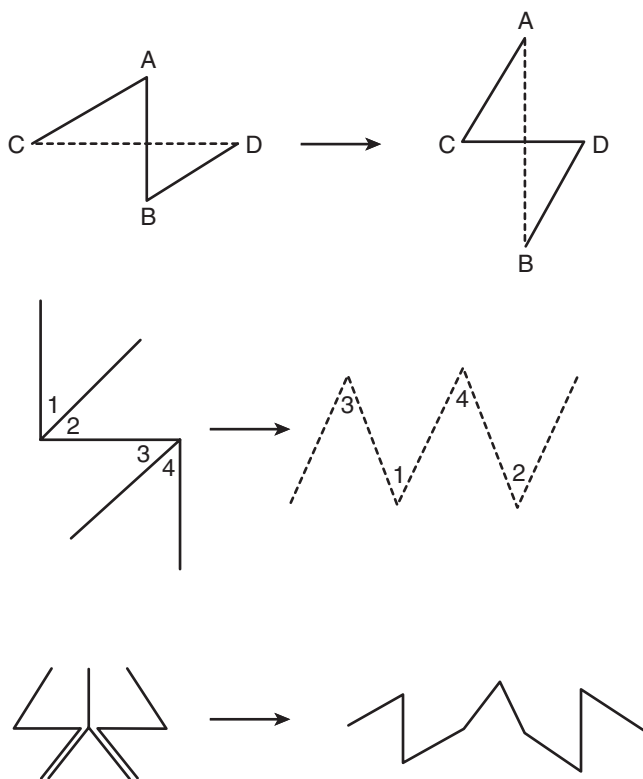


Figure 45-2. Schematic of the Z-plasty technique. *Top:* Simple Z-plasty. *Middle:* Four-flap Z-plasty. *Bottom:* Five-flap Z-plasty. (Modified with permission from Hudson DA: *Some thoughts on choosing a Z-plasty: The Z made simple.* *Plast Reconstr Surg.* 2000;106:665.)

release factor III (thromboplastin), which accelerates the clotting cascade. Clotting factors in the plasma are activated, and the coagulation cascade forms thrombin and eventually fibrin. Simultaneously, the complement system activates and produces chemoattractive complement protein fragments. Platelets, activated by thrombin and exposed collagen, release a number of growth factors and cytokines. Traumatized vessels contract in response to both direct physical stimulation and prostaglandins released by platelets. Intact local microvasculature vasodilates and leaks plasma in response to inflammatory mediators such as

histamine, kinins, and serotonin. These early events, and others, establish inflammation and, finally, homeostasis.³

Platelet activation initiates the first major escalation in the inflammatory response. Within minutes, platelets release signaling molecules from their α -granules to attract macrophages, polymorphonuclear cells (PMNs), fibroblasts, and vascular endothelial cells. Within a few hours of injury, PMNs and macrophages invade the wound and remove tissue debris, coagulation proteins, and bacteria. Although both PMNs and macrophages begin to marginate early, PMNs dominate during the first few days. PMNs also constitute the primary defense against invading organisms that have breached the epithelial barrier. PMNs and macrophages, in concert with the complement system, form the basis of “natural” or “nonspecific” immunity. If there is no infection or foreign material, the neutrophil population diminishes by the second day, whereas macrophages continue to amass.³

Macrophages become the major population by the third day after injury. These cells then dominate the wound region for days to weeks. Macrophages are the “masterminds” behind the finely tuned array of repair events that characterizes the proliferative phase of healing. Like neutrophils, activated macrophages continue the task of wound débridement. They are a rich source of degradative enzymes that process the extracellular matrix to make room for remodeling. Tightly coordinated release of the many growth factors, colony-stimulating factors, interleukins, interferons, and cytokines gives the macrophage the ability to regulate migration, proliferation, and specific protein synthesis of multiple cell lines. Macrophages lead the procession of new tissue into the wound dead space. Immature, replicating fibroblasts follow the macrophages. Mature fibroblasts then advance into the wound and are, in turn, followed by newly forming capillary buds, the last cells in the procession.³

Thus, injury perturbs the microenvironment and leads to the autoamplifying inflammatory phase. As a result of these processes, three changes occur in the wound: the environment becomes hypoxic, acidotic, and hyperlactated. One biochemical pathway by which this low redox potential state can signal cells to take biologic action is the adenosine diphosphoribose (ADPR) system. Recent evidence has shown that alterations of the polyADPR system affect regulation of collagen and vascular endothelial growth factor (VEGF) transcription.³ Consequently, the metabolic state that is so deranged in the wound microenvironment is intimately linked to altered cellular function and leads to reparative cell phenotypes.

After inflammation has begun, fibroblasts are attracted by many stimuli and then proliferate and migrate into the site of injury. Fibroblasts are the major producers of collagen in the repair response. Substances that increase collagen deposition and maturation include lactate, oxygen, and growth factors. Lack of these agents as well as steroid treatments decrease collagen in wounds.

Macrophages also usher along angiogenesis, largely through the release of VEGF. VEGF production is upregulated by the same wound metabolic environment that stimulates collagen production. As neovascularization takes place, many of the conditions that signaled the start of the inflammatory and proliferative phases are resolved, and the wound healing response recedes.

Epidermal cells are attracted to the healing wound by the same cytokines that attract other wound cells. Epithelialization proceeds best in a moist environment with high oxygen tension.³

Table 45-1

Tissue lengthening with Z-plasty

TYPE OF Z-PLASTY	INCREASE IN LENGTH OF CENTRAL LIMB (%)
Simple 45°	50
Simple 60°	75
Simple 90°	100
Four-flap with 60° angles	150
Double-opposing	75
Five-flap	125

Source: Modified with permission from Hudson DA. *Some thoughts on choosing a Z-plasty: the Z made simple.* *Plast Reconstr Surg.* 2000;106:665.

Table 45-2

Preoperative management

- Assess and optimize cardiopulmonary function; correct hypertension.
- Treat vasoconstriction: attend to blood volume, thermoregulatory vasoconstriction, pain, and anxiety.
- Assess recent nutrition and provide treatment as appropriate.
- Treat existing infection.
- Assess wound risk using the SENIC index.
- Start administration of vitamin A in patients taking glucocorticoids.
- Maintain tight blood glucose control.

SENIC = Study on the Efficacy of Nosocomial Infection Control.

Source: Modified with permission from Hunt TK, Hopf HW. Wound healing and wound infection: what surgeons and anesthesiologists can do. *Surg Clin North Am.* 1997;77:587. Copyright Elsevier.

Preoperative, intraoperative, and postoperative interventions may be taken by the surgeon to minimize infection and optimize wound healing (Tables 45-2–45-4). These measures all draw on what we understand of the physiologic wound healing process.

Skin Grafts and Skin Substitutes

Skin is comprised of 5% epidermis and 95% dermis. The dermis contains sebaceous glands, whereas sweat glands and hair follicles are located in the subcutaneous tissue. The dermal thickness and concentration of skin appendages vary widely from one location to another on the body. The skin vasculature is superficial to the superficial fascial system and parallels the skin surface. The cutaneous vessels branch at right angles to penetrate subcutaneous tissue and arborize in the dermis, finally forming capillary tufts between dermal papillae.⁴

Skin grafting techniques date back >3000 years to India, where forms of the technique were used to resurface nasal defects in thieves who were punished for their crimes with nose amputation. Modern skin grafting methods include split-thickness grafts, full-thickness grafts, and composite tissue

Table 45-3

Intraoperative management

- Administer appropriate prophylactic antibiotics at start of procedure. Keep antibiotic levels high during long operations.
- Keep patient warm.
- Maintain gentle surgical technique with minimal use of ties and cautery.
- Keep wounds moist.
- Perform irrigation in cases of contamination.
- Elevate tissue oxygen tension by increasing the level of inspired oxygen.
- Delay closure of heavily contaminated wounds.
- Use appropriate sutures (and skin tapes).
- Use appropriate dressings.

Source: Modified with permission from Hunt TK, Hopf HW. Wound healing and wound infection: what surgeons and anesthesiologists can do. *Surg Clin North Am.* 1997;77:587. Copyright Elsevier.

Table 45-4

Postoperative management

- Keep patient warm.
- Provide analgesia to keep patient comfortable, if not pain free.
- Keep up with third-space losses. Remember that fever increases fluid losses.
- Assess perfusion and react to abnormalities.
- Avoid diuresis until pain is gone and patient is warm.
- Assess losses (including thermal losses) if wound is open.
- Assess need for parenteral/enteral nutrition and respond.
- Continue to control hypertension and hyperglycemia.

Source: Modified with permission from Hunt TK, Hopf HW. Wound healing and wound infection: what surgeons and anesthesiologists can do. *Surg Clin North Am.* 1997;77:587. Copyright Elsevier.

grafts (Table 45-5). Each technique has advantages and disadvantages. Selection of a particular technique depends on the requirements of the defect to be reconstructed, the quality of the recipient bed, and the availability of donor site tissue.

Split-Thickness Grafts. Split-thickness skin grafting represents the simplest method of superficial reconstruction in plastic surgery. Many of the characteristics of a split-thickness graft are determined by the amount of dermis present. Less dermis translates into less primary contraction (the degree to which a graft shrinks in surface area after harvesting and before grafting), more secondary contraction (the degree to which a graft shrinks during healing), and better chance of graft survival. Thin split grafts have low primary contraction, high secondary contraction, and high reliability of graft take, often even in imperfect recipient beds. Thin grafts, however, tend to heal with abnormal pigmentation and poor durability compared with thick split grafts and full-thickness grafts. Thick split grafts have more primary contraction, less secondary contraction, and may take less hardily. Split grafts may be meshed to expand the surface area that can be covered. This technique is particularly useful when a large area must be resurfaced, as in major burns.

Table 45-5

Classification of skin grafts

TYPE	DESCRIPTION	THICKNESS (IN)
Split thickness	Thin (Thiersch-Ollier)	0.006–0.012
	Intermediate (Blair-Brown)	0.012–0.018
	Thick (Padgett)	0.018–0.024
Full thickness	Entire dermis (Wolfe-Krause)	Variable
Composite tissue	Full-thickness skin with additional tissue (subcutaneous fat, cartilage, muscle)	Variable

Source: Modified with permission from Andreassi A, Bilenchi R, Biagioli M, et al. Classification and pathophysiology of skin grafts. *Clin Dermatol.* 2005;23:332. Copyright Elsevier.

Meshed grafts usually also have enhanced reliability of engraftment, because the fenestrations allow for egress of wound fluid and excellent contour matching of the wound bed by the graft. The fenestrations in meshed grafts reepithelialize by secondary intention from the surrounding graft skin. The major drawbacks of meshed grafts are poor cosmetic appearance and high secondary contraction. Meshing ratios used usually range from 1:1.5 to 1:6, with higher ratios associated with magnified drawbacks.

Full-Thickness Grafts. By definition, full-thickness skin grafts include the epidermis and the complete layer of dermis. The subcutaneous tissue is carefully removed from the deep surface of the dermis to maximize the potential for engraftment. Full-thickness grafts are associated with the least secondary contraction upon healing, the best cosmetic appearance, and the highest durability. As a result, they are frequently used in reconstructing superficial wounds of the face and the hands. These grafts require pristine, well-vascularized recipient beds without bacterial colonization, previous irradiation, or atrophic wound tissue.

Graft Take. Skin graft take occurs in three phases: imbibition, inosculation, and revascularization. Plasmatic imbibition refers to the first 24 to 48 hours after skin grafting, during which time a thin film of fibrin and plasma separates the graft from the underlying wound bed. It remains controversial whether this film provides nutrients and oxygen to the graft or merely a moist environment to maintain the ischemic cells temporarily until a vascular supply is reestablished. After 48 hours, a fine vascular network begins to form within the fibrin layer. These new capillary buds interface with the deep surface of the dermis and allow for transfer of some nutrients and oxygen. This phase, called *inosculation*, transitions into revascularization, the process by which new blood vessels either directly invade the graft or anastomose to open dermal vascular channels and restore the pink hue of skin. These phases are generally complete by 4 to 5 days after graft placement. During these initial few days, the graft is most susceptible to interference in engraftment caused by infection, mechanical shear forces, and hematoma or seroma.⁴

Composite Grafts. Composite tissue grafts are donor tissue containing more than just epidermis and dermis. They commonly include subcutaneous fat, cartilage and perichondrium, and muscle. Although less common than skin grafts, grafts of this type are particularly useful in select cases of nasal reconstruction. Excision of the thick skin of the nasal lobule may create too deep a defect to reconstruct with a full-thickness skin graft. The ear lobe composite graft provides thicker coverage with good color match and a fairly inconspicuous donor site (Fig. 45-3). Similarly, the root of the helix of the ear may be used to reconstruct the alar rim, providing skin coverage, cartilaginous support, and internal lining in a single technique.

Flaps

A flap is a vascularized block of tissue that is mobilized from its donor site and transferred to another location, adjacent or remote, for reconstructive purposes. The difference between a graft and a flap is that a graft brings no vascular pedicle and derives its blood flow from recipient site revascularization, whereas a flap arrives with its blood supply intact.

Random Pattern Flaps. Random pattern flaps have a blood supply based on tiny blood vessels in the dermal-subdermal

plexus, as opposed to the discrete, well-described vessels of axial pattern flaps (Fig. 45-4).⁵ Random flaps are typically used to reconstruct relatively small, full-thickness defects that are not amenable to skin grafting. Unlike axial pattern flaps, random flaps are limited by their geometry. The generally accepted reliable length-to-width ratio for a random flap is 3:1. Exceptions to this rule abound, however. There are many different types of random cutaneous flaps that differ in geometry and mobility. A *transposition flap* is rotated about a pivot point into an adjacent defect (Fig. 45-5). A *Z-plasty* is a type of transposition flap in which two flaps are rotated, each into the donor site of the other, to achieve central limb lengthening (see Fig. 45-2). Another common transposition flap is the *rhomboid (Limberg) flap* (Fig. 45-6). *Rotational flaps* are similar to transposition flaps but differ in that they are semicircular (Fig. 45-7). *Advancement flaps* slide forward or backward along the flap's long axis. Two common variants include the rectangular advancement flap and the V-Y advancement flap (Fig. 45-8). Like transposition flaps, *interpolation flaps* rotate about a pivot point. Unlike transposition flaps, they are inset into defects near, but not adjacent, to the donor site. An example of an interpolation flap is the thenar flap for fingertip reconstruction (Fig. 45-9).

Fasciocutaneous and Myocutaneous Flaps. The *composition* of a flap describes its tissue components. For example, a cutaneous flap contains skin accompanied by a variable amount of subcutaneous fat. A fasciocutaneous flap contains skin and fascia, whereas an adipofascial flap contains subcutaneous fat and fascia without overlying skin. A muscle flap contains muscle only, whereas a myocutaneous flap also contains the overlying skin and intervening tissues. An osseous flap contains vascularized bone only, whereas an osteomyocutaneous flap contains, in addition, muscle, skin, and subcutaneous tissues.

The *contiguity* of a flap describes its position related to its source. Local flaps are transferred from a position adjacent to the defect. Regional flaps are from the same anatomic region of the body as the defect (e.g., the lower extremity region or the head and neck region). Distant flaps are transferred from a different anatomic region to the defect. They may remain attached to the source anatomic region (*pedicled flaps*) or may be transferred as *free flaps* by microsurgery. These are completely detached from the body, and their blood supply is reinstated by microvascular anastomoses to recipient vessels close to the defect.

The term *pedicle* was originally used to describe a bridge of tissue that remained between a flap and its source, similar to how a peninsula remains attached to its mainland. However, as knowledge of flap blood supply and (micro)vascular anatomy has improved over the years, the term pedicle has increasingly become reserved for describing the blood vessels that nourish the flap. Thus its current use is, in essence, *vascular pedicle* in shortened form. As a refinement, it is possible to dissect the pedicle free of its surrounding tissues (termed *skeletonization*) to allow any tortuosity of the supplying blood vessels to be released in order to maximize their reach toward a given defect. This is usually performed in a retrograde direction starting from where the pedicle enters the flap tissues. Similarly, it is possible to detach the desired skin paddle circumferentially from all unneeded surrounding tissues in order to maximize the freedom with which the flap can be inset to reconstruct the defect. Hence, a *pedicled island* flap has had its cutaneous component circumferentially incised while preserving its vascular pedicle. Therefore, a free flap and a pedicled island flap differ only in

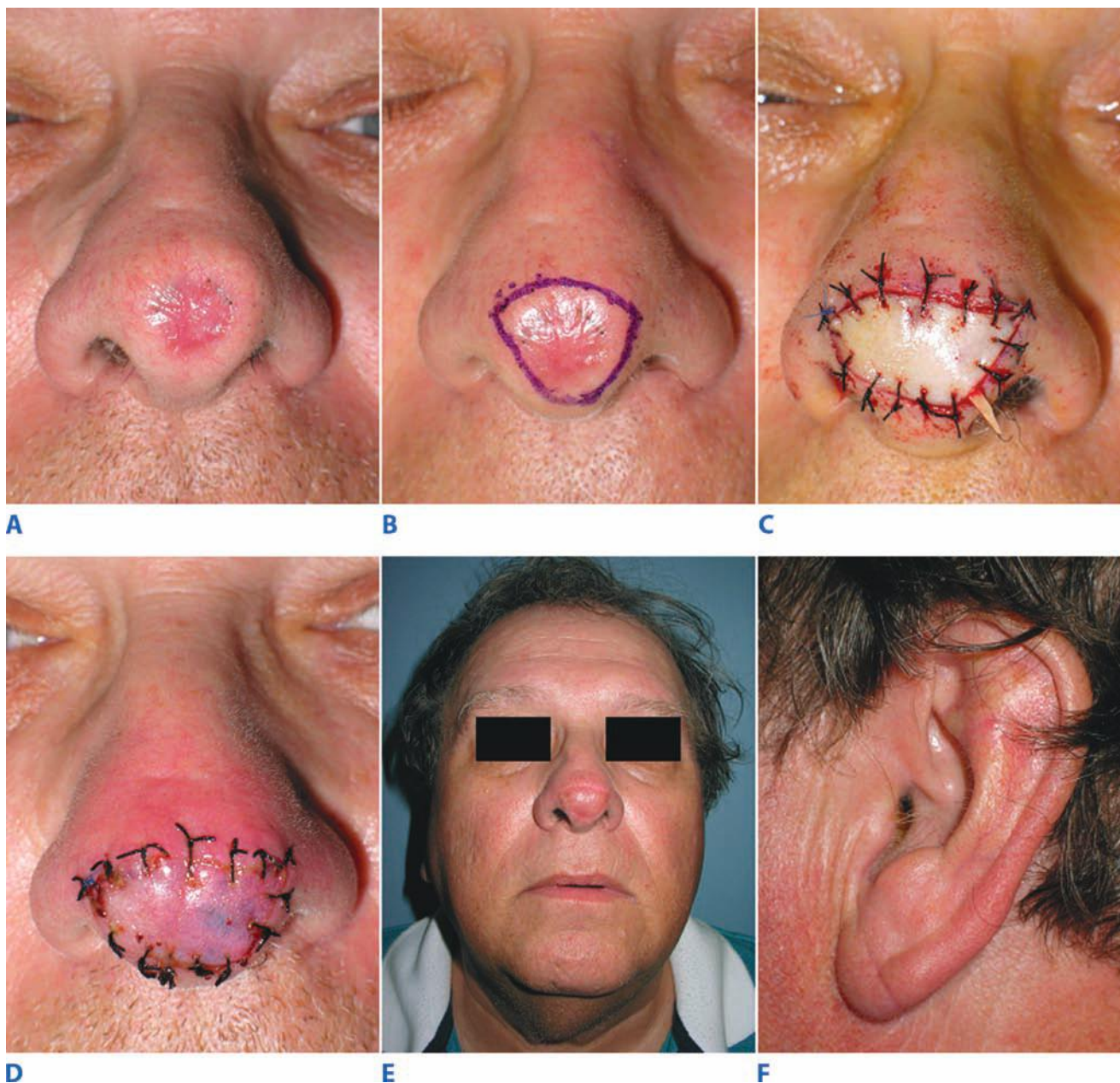


Figure 45-3. Composite graft reconstruction of nasal lobule. **A.** Scarred lobule from previous lesion excision. **B.** Scar excision markings. **C.** Insetting of composite ear lobe skin and subcutaneous fat graft. **D.** Postoperative day 3; note the pink hue of revascularization. **E.** Appearance at 5 weeks postoperatively. **F.** Donor site at 5 weeks postoperatively.

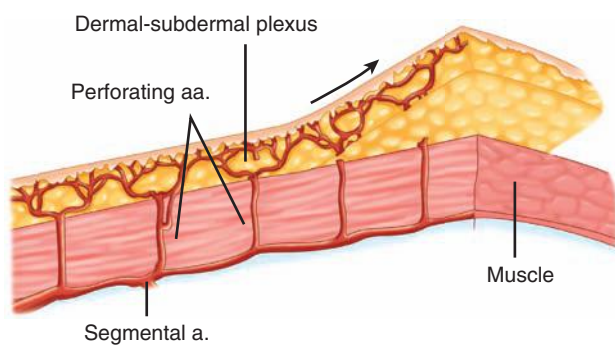


Figure 45-4. Random pattern flap architecture. a. = artery. (Reproduced with permission from Aston *et al.*⁵)

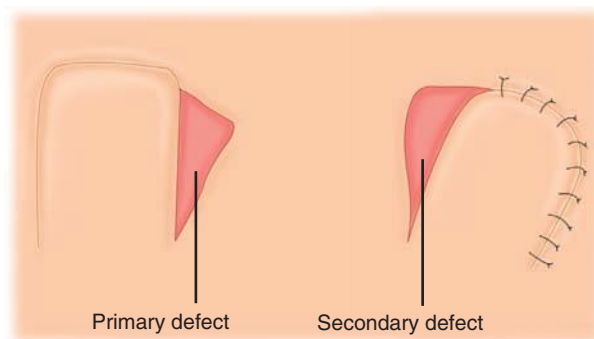


Figure 45-5. Random pattern transposition flap.

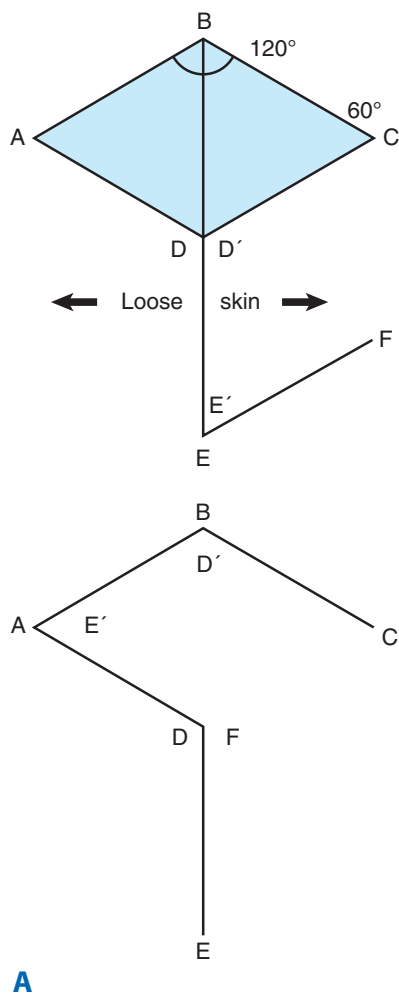


Figure 45-6. A and B. Random pattern transposition flap, the rhomboid flap. (Photographs reproduced with permission from M. Gimbel.)

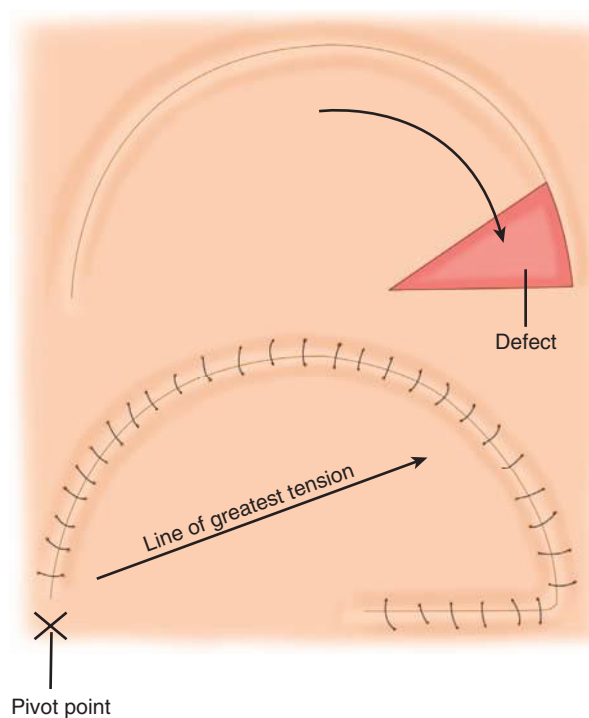


Figure 45-7. Random pattern rotational flap. (Reproduced with permission from Aston et al.⁵)

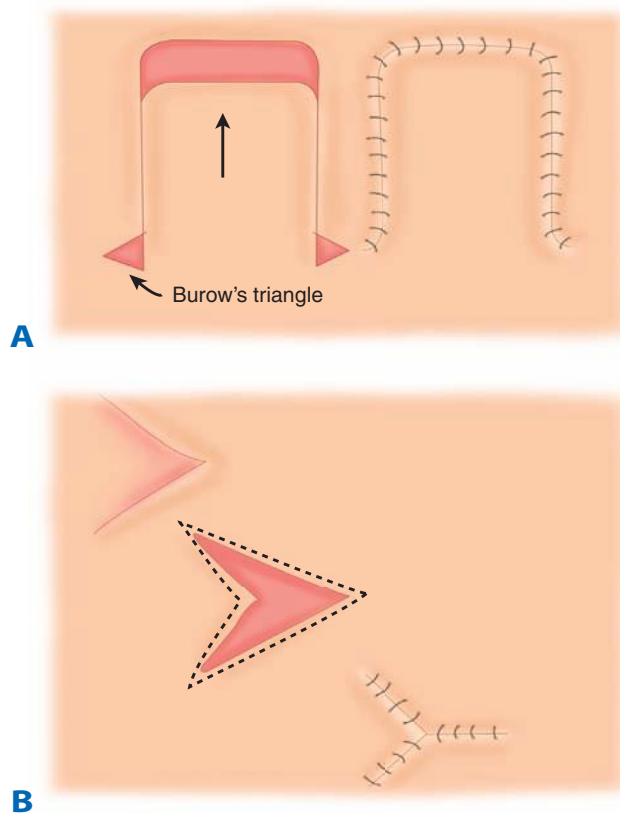


Figure 45-8. Random pattern advancement flap. A. Rectangular advancement flap with Burow's triangle excision. B. V-Y advancement flap. (Reproduced with permission from Aston et al.⁵)

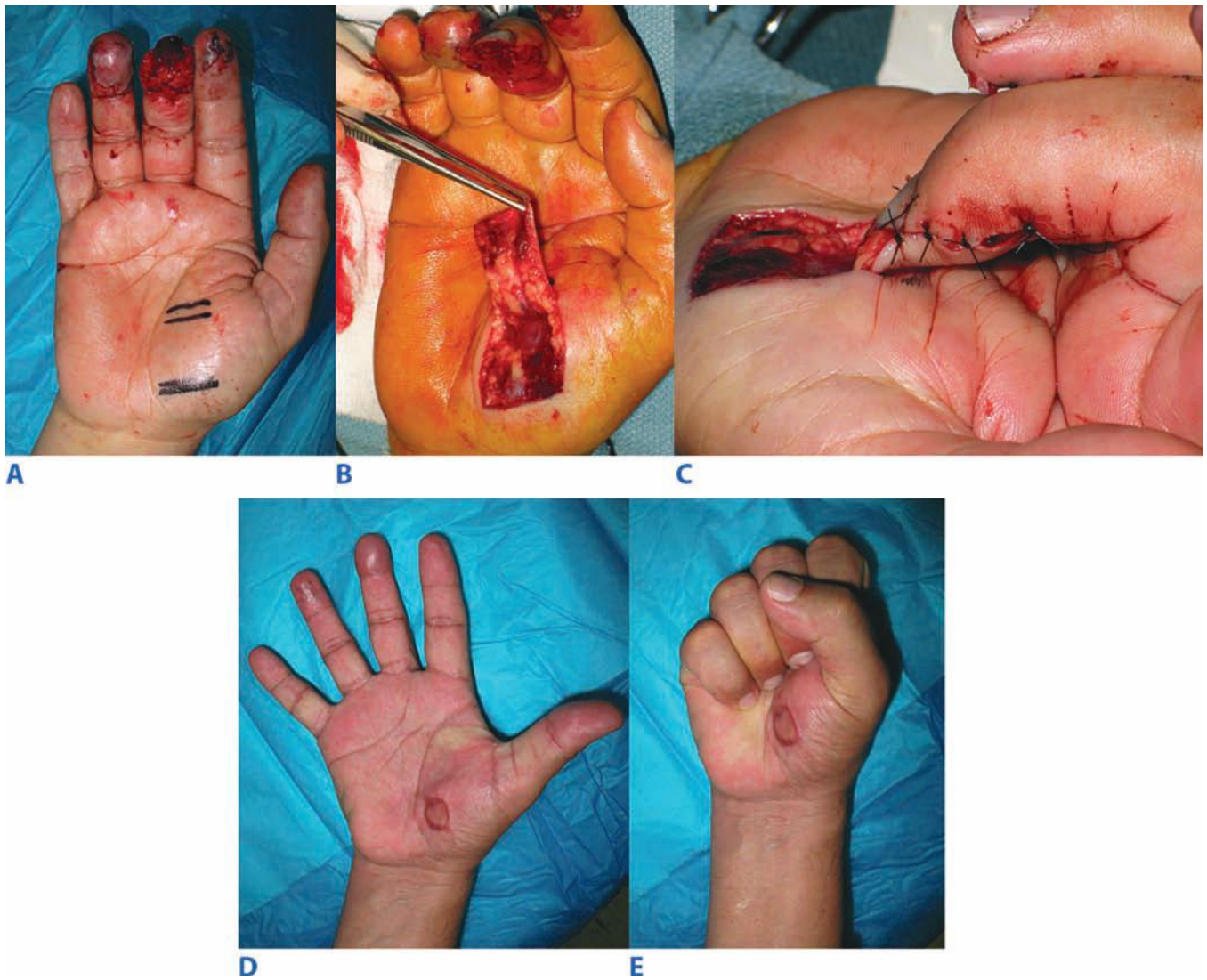


Figure 45-9. Random pattern interpolation flap—the thenar flap. **A.** Middle fingertip injury with exposed bone and tendon. **B.** Elevation of distally based random pattern thenar flap. **C.** Insetting. **D** and **E.** Function and form at 3 months, after skin grafting of donor site. (Photographs reproduced with permission from M. Gimbel.)

that the former requires transection of the vascular pedicle for anastomosis to alternative recipient vessels, whereas the pedicle of the latter remains in continuity.

Such flaps that are supplied by an anatomically defined configuration of vessels are described as having an *axial pattern* blood supply and can be transferred as local, regional, or distant, and pedicled, island pedicled, or free flaps.⁶ Arising from the aorta are arteries that supply the internal viscera and other deep vessels that divide to form the main arterial supplies to the trunk, head, and extremities. They ultimately feed interconnecting vessels that supply the vascular plexuses of the fascia, subcutaneous tissue, and skin. These interconnecting vessels reach the skin via either fasciocutaneous (also called *septocutaneous*) vessels that traverse fascial septae between muscles, musculocutaneous perforators that penetrate muscle bellies, or direct cutaneous vessels that traverse neither muscle bellies nor fascial septae.⁷ Axial pattern flaps, incorporating suprafascial tissues, are supplied by these fasciocutaneous (septocutaneous), musculocutaneous, or direct cutaneous arteries. The internal viscera are also a source of axial pattern flaps, such as the jejunum

flap and omentum flap. The circulation of bone- and muscle-containing flaps also is mainly axial in pattern. It also is possible to design local flaps, such as V-Y advancements and rhomboid flaps, as axial pattern flaps. In contrast to axial pattern flaps, random pattern flaps are only commonly transferred as local flaps by virtue of their lack of a defined vascular pedicle and cannot be transferred as island pedicled or free flaps. Axial pattern flaps may possess some areas with random pattern circulation, usually located at the flap periphery.

The volume of tissue reliably vascularized by the pedicle of an axial pattern flap defines its limits. In other words, the portion of a flap that extends beyond the capabilities of its vascular pedicle to perfuse it reliably will ordinarily undergo necrosis of that portion. This can be clarified conceptually. The arterial tree can be described in terms of its *angiosomes*.⁸ An angiosome is a block of tissue that is reliably supplied by a given artery. Neighboring angiosomes overlap, just as the dermatomes of neighboring nerves overlap. An anatomic angiosome is defined by the limits of an artery's ramifications, where it forms anastomoses with a neighboring anatomic angiosome. The vessels that pass

between these anatomic angiosomes are called *choke vessels*. In life, these may open or close in response to physiologic changes to increase or decrease, respectively, an artery's *dynamic angiosome* momentarily. Accordingly, at any given time point, the dynamic angiosome of an artery may be approximated by the volume of tissue stained by an intravascular administration of fluorescein into that artery (indicating the reach of blood flow from that artery into tissues). The *potential angiosome* of an artery is the volume of tissue that can be included in a flap that has undergone *conditioning* (see below). Both the dynamic and potential angiosomes extend beyond the anatomic angiosome of an artery. Although the angiosomal concept provides some guidance to the size and volume limits of a flap harvest, there remains no quantifiable method to predict safe flap harvest limits exactly.

Conditioning refers to any procedure that increases the reliability of a flap by enlarging the angiosome of the pedicle artery from its dynamic toward its potential angiosome. Invoking the *delay phenomenon*, for example, has improved the survival of flaps that otherwise would more frequently be complicated by unpredictable partial necrosis, such as the pedicled transverse rectus abdominis myocutaneous (TRAM) flap. The procedure can be particularly useful in patients at higher risk, such as those who are obese, smoke, or have received radiotherapy. One method of delay for the pedicled TRAM flap is to divide a major portion of its blood supply, the deep inferior epigastric artery on both sides, approximately 2 weeks before transfer. In response, blood from the anatomic angiosome of the superior epigastric artery appears to flow into that of the interrupted deep inferior epigastric artery via intervening choke vessels. As a result, the flap becomes conditioned to rely on the superior epigastric artery. The TRAM flap can then be transferred based on the superior epigastric artery with less risk of its distal portions becoming ischemic and possibly necrotic. Several theories have been proposed to explain the delay phenomenon, including metabolic compensatory responses to relative ischemia and dilatation of choke vessels; however, its mechanisms remain incompletely understood.⁹

Further subclassifications of flap circulation have been introduced for muscular and fasciocutaneous flaps.¹⁰ Individual muscles have been classified by Mathes and Nahai into five types (I–V) according to their blood supply (Table 45-6). This classification is also applied to the respective myocutaneous flaps. Fasciocutaneous flaps also have been classified by these authors into types A, B, and C (Table 45-7). The inclusion of muscle in a flap may serve to increase flap bulk (so as to obliterate dead space) or to provide a functioning component with the harvest of its motor nerve for coaptation to a recipient motor nerve. The purported advantages of muscle-containing flaps over fasciocutaneous flaps for use in previously infected tissue beds or for fracture healing have been debated.

With progressive advancements in flap transfer techniques and in understanding of microvascular flap anatomy, plastic surgeons have steadily increased the number and variety of available flaps, thereby improving the results of flap reconstructions. In addition, this knowledge has reduced the morbidity associated with flap harvest. Perhaps the most important advancement in flap surgery within recent decades has been the introduction of the perforator flap.¹¹ Perforator flaps evolved from the observation that the muscle component of myocutaneous flaps served as a carrier of blood vessels to the overlying fasciocutaneous tissues. Prior to this, it had been deemed mandatory to include the

Table 45-6

Mathes-Nahai classification of muscular flaps

CLASSIFICATION	VASCULAR SUPPLY	EXAMPLE
Type I	One vascular pedicle	Gastrocnemius
Type II	Dominant and minor pedicles (the flap cannot survive based only on the minor pedicles)	Gracilis
Type III	Two dominant pedicles	Rectus abdominis
Type IV	Segmental pedicles	Sartorius
Type V	One dominant pedicle with secondary segmental pedicles (the flap can survive based only on the secondary pedicles)	Pectoralis major

muscle for reliable harvest of fasciocutaneous tissues supplied by musculocutaneous perforators, even if it was not necessary to include that muscle for the reconstruction. This unfortunately caused an unnecessary muscular deficit at the donor site, and for this reason, fasciocutaneous flaps that were supplied by musculocutaneous perforators instead of septocutaneous vessels were sometimes abandoned. The introduction of intramuscular retrograde dissection techniques, however, allowed the skeletonization of a musculocutaneous perforator from its encasement within a muscle belly, which spared that muscle from flap harvest and preserved its donor site function.^{7,11} Further refinement of this concept gave rise to the harvest of cutaneous flaps based on any vessel that penetrated the fascia, which preserved the muscle (when the vessel was a musculocutaneous perforator) as well as the fascia (by suprafascial dissection). Within the last decade, free-style flap harvest has also been introduced.¹² With a handheld Doppler ultrasound probe, the surgeon is able to identify an arterial supply to almost any area of skin with the desired reconstructive characteristics and trace that pedicle in retrograde fashion along whatever direction it takes, preserving donor site fascia and muscle as necessary. Although the exact definition of what a perforator flap is remains contentious, its advantages

Table 45-7

Nahai-Mathes classification of fasciocutaneous flaps

CLASSIFICATION	VASCULAR SUPPLY	EXAMPLE
Type A	Direct cutaneous vessel that penetrates the fascia	Temporoparietal fascial flap
Type B	Septocutaneous vessel that penetrates the fascia	Radial artery forearm flap
Type C	Musculocutaneous vessel that penetrates the fascia	Transverse rectus abdominis myocutaneous flap

remain clear: reduced donor site morbidity, reduced flap bulk, and increased flexibility in choosing desired flap components for reconstruction. The circulation of perforator flaps is axial in pattern; consequently, they can be transferred as pedicled island flaps or by microvascular free tissue transfer.

Free Tissue Transfer

A free tissue transfer, often referred to as a *free flap* procedure, is an autogenous transplantation of vascularized tissues. Any axial pattern flap with pedicle vessels of a suitable diameter can be transferred as a free flap. This involves three main steps: (a) complete detachment of the flap, with devascularization, from the donor site; (b) revascularization of the flap with anastomoses to blood vessels in the recipient site; and (c) an intervening period of flap ischemia. Flap circulation must be restored within a tolerable ischemia time.

Given the small diameter of most flap pedicle vessels (usually between 0.8 and 4.0 mm), these anastomoses are usually performed using an operative microscope that provides dedicated illumination and between 6× and 40× magnification. Any surgery performed with the aid of an operative microscope is termed *microsurgery*; such anastomoses are therefore termed *microvascular anastomoses*. High-magnification surgical loupes are usually used for flap harvest, especially for dissecting the flap pedicle, because they allow greater operator freedom. Aside from microvascular anastomosis, microsurgical techniques include microneural coaptation, microlymphatic anastomosis, and microtubular anastomosis.

The first successful free tissue transfer in humans was of a jejunal free flap for cervical esophagus reconstruction in 1957; however, the surgeons did not use microsurgery for the anastomoses. The first *microvascular* free tissue transfers in humans were carried out during the late 1960s and early 1970s. Free flaps were initially considered to be a last-resort option to reconstruct the most complex defects. However, as a result of improved microsurgical techniques and microinstrumentation, as well as proper patient and free flap selection and effective postoperative monitoring methods, the success rates have increased to exceed 95%.¹³ Today, free tissue transfer is often the first-choice treatment for many defects and is no longer considered the last-ditch effort. It is now ubiquitously used in appropriate patients by reconstructive plastic surgeons worldwide.

The predetermining factor in free flap failure is occlusion of its blood supply due to thrombosis. As enumerated by Virchow’s triad, any factors that alter normal laminar blood flow, cause endothelial damage, or change the constitution of blood (producing hypercoagulability) increase the risk of

thrombosis (Table 45-8).¹⁴ Avoidance of this complication, therefore, begins with a thorough patient evaluation for the presence of acquired or inherited thrombophilic tendencies. The patient’s hemodynamic status influences that of the free flap and should be optimized. The effect of tobacco smoking on free flap success has been debated, with some larger retrospective studies reporting no difference in thromboembolic complications; however, smoking is well known to affect wound healing.^{13,15} Smoking and the use of potentially vasoconstrictive agents, such as caffeine, should be avoided for several weeks before and after a free flap procedure. The restoration of normal laminar blood flow and avoidance of endothelial damage are addressed principally by careful flap inseting and meticulous microvascular surgical technique.

Planning a free flap goes beyond a simple calculation of matching flap and defect dimensions and tissue characteristics. The surgeon must, in addition, consider several important technicalities: what flap pedicle length and size are required (affected by flap choice); which recipient vessels to use; how to orient anastomoses (end to end or end to side), deal with mismatched donor and recipient vessel dimensions, overcome unhealthy donor and/or recipient vessels (e.g., traumatic dissection, scarred surgical field due to previous operation or radiotherapy), inset flap tissues (to maximize functional and cosmetic results without detriment to flap circulation), route the pedicle (to restore normal blood flow without pedicle kinking, twisting, or compression), position the patient (especially if the flap is to be inset over mobile soft tissue or joints), and place postoperative dressings (so as to produce no compression of the flap or pedicle); and what donor site morbidity will likely result (there is a risk-benefit decision between defect severity and flap choice).¹⁶ In addition, the surgeon must have a suitable backup plan to overcome intraoperative troubles; for example, insufficient pedicle length can be addressed with an interpositional vein graft adjoining the donor and recipient vessels, and iatrogenic vessel injury or severely aberrant anatomy may necessitate use of a backup flap or backup recipient vessels.¹³

A clear understanding of the blood supply to the free flap and its tissue components is a prerequisite to harvesting a viable free flap. Pedicle vessels must be identified and protected and handled minimally and atraumatically to avoid thrombogenic factors (see Table 45-8). Meticulous technique also reduces the risk of vasospasm, but the latter can be ameliorated by topical lidocaine or papaverine should it occur. Critical vessels connecting flap components must also be recognized and preserved. Under microscope magnification, the donor and recipient

Table 45-8
Thrombogenic factors that can affect free flap pedicles and anastomoses

ALTERED LAMINAR BLOOD FLOW	ENDOTHELIAL DAMAGE	HYPERCOAGULABILITY
Tension or intimal malalignment at the anastomosis site; twisting, kinking, compression, or vasospasm of pedicle vessels	Iatrogenic damage (e.g., back-walled anastomotic suture, poor vessel handling, too many sutures)	Acquired thrombophilic tendency (e.g., pregnancy, paraneoplastic Trousseau’s syndrome, antiphospholipid antibody syndromes)
Intraluminal structures (e.g., atherosclerotic plaque, venous valves, back-walled anastomotic suture)	Previous vessel damage (e.g., atherosclerosis, trauma)	Hereditary thrombophilias (e.g., activated protein C resistance, protein C/protein S deficiency, hyperhomocysteinemia)

vessels should be dissected back to health. The presence of, for example, venous valves, atherosclerotic plaques, intimal trauma, and intraluminal prolapse of adventitial tissue at or adjacent to the anastomosis site increases the risk of thrombosis. The vessel ends should be cleared of periadventitial tissues for 3 to 5 mm with sharp dissection under the microscope. Periadventitial dissection should be limited to this extent, so as to avoid potential devascularization of the vessel wall by removal of the vasa vasorum and prevent the subsequent delayed development of a perianastomotic pseudoaneurysm. Adventitiectomy also helps relieve vasospasm by increasing compliance of the vessel wall and by inducing a local sympathectomy effect. The vessel ends usually are stabilized with a double approximating microvascular clamp for anastomosis. Interrupted sutures or, less commonly, continuous sutures can accomplish the anastomosis. The microneedle typically has a three-eighths circle curvature and is between 30 and 150 μm in size. Its monofilament microsuture is usually between 9-0 and 11-0 caliber. The dimensions of the vessels to be anastomosed define the choice of microneedle and microsuture. Less commonly, suture alternatives such as fibrin adhesives or laser welding (these remain largely experimental) and mechanical anastomotic devices (e.g., venous couplers) may be used. Triangulating or bisecting suturing techniques can help to achieve an even placement of sutures. Normally, each suture should include the full thickness of both vessel walls, none should catch the opposite vessel wall (which causes disastrous luminal occlusion and intimal trauma), and the size of each bite should approximate the vessel wall thickness. The configuration of the anastomosis can be either end-to-end (Fig. 45-10), if the distal circulation can be adequately preserved, or end-to-side (Fig. 45-11), if the distal circulation must be preserved, as in the case of an extremity supplied by one dominant vessel. An end-to-side orientation may also be useful to overcome dramatically mismatched donor-recipient vessel dimensions. Whatever the method chosen, microanatomic differences between the vessels should be respected so as to achieve accurately approximated

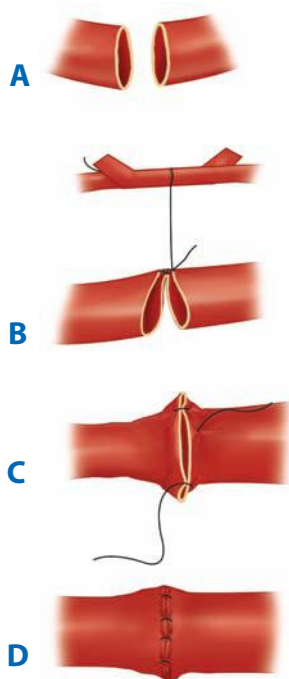


Figure 45-10. A through D. End-to-end anastomosis.

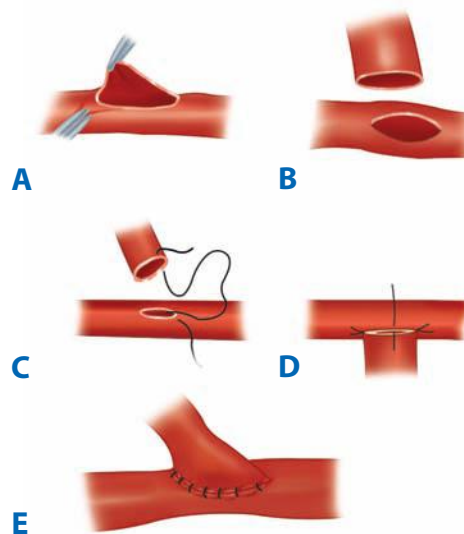


Figure 45-11. A through E. End-to-side anastomosis.

intimal surfaces in a tension-free anastomosis, devoid of redundancy that might promote kinking.¹³

The clinical monitoring of a free flap should start during flap harvest, especially before its pedicle is divided. A free flap that is struggling to maintain normal perfusion characteristics during harvest most likely has insufficient circulation, which may be due to arterial or venous compromise or a combination of both (Table 45-9). Flap compromise may be due to reversible factors such as pedicle kinking, tensioning, or twisting; patient hemodynamic compromise; or an overly large flap harvest for the chosen pedicle vessels. If poor flap perfusion continues despite the absence or correction of all these factors, an inherent flap problem or a critical vascular injury to the flap or its pedicle must be considered, and it may not be safe to continue its harvest. This is one example of a situation in which a backup plan may require execution.

Clinical flap monitoring continues after successful restoration of arterial inflow and venous outflow. The mainstay of postoperative free flap monitoring is clinical assessment (see Table 45-9), although supplementary instrument monitoring

Table 45-9

Clinical signs of arterial and venous compromise in a free flap^a

CLINICAL SIGN	ARTERIAL COMPROMISE	VENOUS COMPROMISE
Color	Becoming paler	Increasingly reddish or purplish
Temperature	Becoming cooler	Becoming warmer
Tissue turgor	Reducing	Increasing
Capillary refill time	Becoming slower	Becoming faster
Pinprick bleeding	Increasingly sluggish	Quickening (and darkening)

^aNote that venous and arterial compromise may coexist, and one may lead to the other.

also can be helpful. Doppler ultrasound assessment of arterial and venous signals is useful for monitoring buried or concealed flaps. If flap perfusion was healthy before division of its donor site pedicle, then poor perfusion after anastomoses is likely due to either a technical error or insufficient systemic hemodynamics. The latter usually is correctable by ensuring that the patient and the patient's environment are suitably warm and by initiating intravenous colloid challenge or, if indicated, blood transfusion. Numerous potential technical errors, which have been described in the earlier paragraphs on planning and anastomosis technique, may occur. Routine postoperative patient monitoring includes measurement of total fluid inputs, urinary catheter output (which should be >1 mL/kg per hour), core temperature, and arterial blood pressure (systolic pressure should be >100 mmHg), as well as pulse oximetry. The patient and free flap are best monitored in an intensive care setting by experienced staff until both are stable enough for routine ward assessments.¹⁷

Occlusion of the anastomosis most commonly arises from intraluminal thrombosis or from external compression of the pedicle, such as from surrounding tissues, fluid accumulation (e.g., hematoma and tissue edema), or overly tight dressings or skin sutures. Because there is a threshold of ischemia beyond which a flap will sustain irreversible tissue and/or microcirculatory damage, it is important that the early signs of flap circulatory compromise be recognized as quickly as possible and the underlying problem diagnosed and corrected promptly if flap health is to be restored successfully.¹⁷ Different tissues tolerate differing durations of ischemia in correlation with their tissue-specific basal metabolic rate. Although cooling free flaps (to reduce basal metabolic rate) has a variably protective effect in experimental settings, it appears that this practice contributes little to improving free flap success in the clinical setting as long as warm ischemia times are kept to <4 hours for most tissues; exceptions include bowel flaps, which are more susceptible to ischemia.¹³

Given that the predisposing factor for free flap failure is thrombus formation, it is understandable that plastic surgeons have looked to anticoagulant therapies in an effort to improve success rates. Although such drugs, including the dextrans, aspirin, heparins, and also some fibrinolytics, appear beneficial in experimental settings, large clinical trials have failed to show any conclusive associations between their use and either free flap success or failure rates.¹⁸ It seems intuitive to use these drugs for failing free flaps as an adjunctive measure alongside operative reexploration and surgical intervention. The surgeon must be aware of their contraindications and recognize that their side effects, apart from bleeding, are occasionally serious. Venous congestion may be addressed by surgical measures as well as by application of medicinal *Hirudo medicinalis* leeches (with concomitant *Aeromonas hydrophila* prophylaxis) or by chemical "leeching" (topical heparin combined with dermal punctures).

Unfortunately, the "no-reflow" phenomenon is occasionally witnessed and leads to irreversible flap failure. This describes a situation in which no venous return drains into the pedicle vein of the flap, even though adequate arterial inflow passes the arterial anastomoses and is seen to enter the flap tissues. The no-reflow phenomenon sometimes follows an extended ischemic insult and appears to be a self-perpetuating cycle of endothelial cellular swelling, inflammatory vasoconstriction, impaired microcirculatory flow, stasis, microcirculatory thromboses, progressive ischemia, and flap failure.¹³

Despite these potential problems, free flap success rates exceed 95% in experienced hands. There is no doubt that increasing microsurgical experience is critical to improving free flap success rates. The laboratory setting is an excellent environment in which to progress beyond the early portion of one's learning curve through supervised microsurgical training and execution of microvascular anastomoses and microvascular free flap procedures in small animals.

Tissue Expansion

Although skin grafts and local flaps are very useful in reconstructing many superficial defects, they are not without their drawbacks. Both leave donor site defects with cosmetic and/or functional sequelae. Grafts are limited in color match and durability, whereas local flaps may supply insufficient tissue and produce contour irregularities. The advent of tissue expansion has created the potential to increase the amount of local, well-matched tissue that can be advanced or transposed as a flap while decreasing donor site morbidity.

The most common method of skin expansion involves the placement of an inflatable silicon elastomer balloon with an integrated or remote port beneath the skin and subcutaneous tissue followed by serial inflation with saline. After completion of expansion, usually over weeks to months, the expander is removed and the redundant overlying skin may be advanced into an adjacent defect. Expanders are available in a multitude of shapes and sizes that can be tailored to the reconstruction. In breast reconstruction, the tissue expander is replaced with a permanent implant instead of using the tissue as a flap to re-create the volume of the breast mound. Histologically, expanded skin demonstrates thickened dermis with enhanced vasculature and diminished subcutaneous fat. Studies have shown that the skin expansion is due not merely to stretch or creep but also to actual generation of new tissue.¹⁹

The technique of tissue expansion comes with its share of potential complications, including infection, hematoma, seroma, expander extrusion, implant failure, skin necrosis, pain, and neurapraxia. Furthermore, an inflated expander is a very visible, albeit temporary, deformity that may cause patients much distress.

Despite these imperfections, tissue expansion has become a major treatment modality in the management of giant congenital nevi, secondary reconstruction of extensive burn scars, scalp reconstruction, and breast reconstruction. The technique has permitted the plastic surgeon to perform reconstructions with tissue of similar color, texture, and thickness with minimal donor site morbidity.

PEDIATRIC PLASTIC SURGERY

Cleft Lip and Palate

Orofacial clefting is the most common congenital anomaly and is known to occur in 1 in 500 live white births.²⁰ The incidence is lower in African Americans and higher in Native Americans and Asians. Clefting of the lip and/or palate is felt to occur around the eighth week of embryogenesis, either by failure of fusion of the medial nasal process and the maxillary prominence or by failure of mesodermal migration and penetration between the epithelial bilayer of the face. The cause of orofacial clefting is felt to be multifactorial. Factors that likely increase the incidence of clefting include increased parental age, drug use and infections during pregnancy, smoking during pregnancy, and

a family history of orofacial clefting. The increased chance of clefting when there is an affected parent is approximately 4%.

The *primary palate* is defined as all tissue anterior to the incisive foramen, including the anterior hard palate (premaxilla), alveolus, lip, and nose. The secondary palate includes everything posterior to the incisive foramen, including the majority of the hard palate and the soft palate (velum). Clefting can involve the lip and nose, with or without a palatal cleft. Clefts of the lip and/or palate are first classified as unilateral or bilateral and then as complete or incomplete (Fig. 45-12). Complete clefts of the lip affect the entire lip and extend up into the nose. Incomplete clefts affect only a portion of the lip and contain a bridge of tissue connecting the central and lateral lip elements, referred to as *Simonart's band*.

Treatment Protocol. Considerable controversy remains over the details of the timing, technique, and protocol for treating children with orofacial clefting. The treatment protocol described in this chapter is accepted at many large cleft centers around the United States. All infants born with cleft-craniofacial anomalies benefit from care by a specialized team dedicated to the treatment of congenital anomalies. Today, this is widely accepted as the standard of care. Often, patients are seen prenatally after a diagnosis is made using sophisticated antenatal ultrasonography. The prenatal consultation has proven to be beneficial to parents, serving to dispel fears and uncertainties, and assuring them that treatment exists. After the infant's birth, a team evaluation occurs, and input is obtained from the surgeon, speech and language pathologist, social worker, craniofacial orthodontist, geneticist, otorhinolaryngologist, and pediatrician. For infants born with orofacial clefting, initial concerns relate to successful feeding and breathing. Infants with palatal clefts cannot generate negative pressure when suckling and therefore need milk dispensed into their mouths from a specialized nurser when they make suckling motions.

Once adequate nutrition and a safe airway are ensured, attention is turned to the cleft anomaly. Attempts to lessen the deformity and set the stage for the surgical repair of the lip and nose begin with a process known as *presurgical infant orthopedics (PSIO)*, which includes procedures such as nasoalveolar molding (NAM) (Fig. 45-13). NAM repositions the neonatal alveolar segments, brings the lip elements into close approximation, stretches the deficient nasal components, and turns wide complete clefts into the morphology of narrow "incomplete" clefts. After PSIO with NAM, the definitive single-stage cleft lip and nose repair is performed at 3 to 6 months of age. With this initial operation, the lip deformity is repaired and a primary nasoplasty reconstructs the cleft lip nasal deformity. If the family does not have access to PSIO or have the resources for this time-intensive therapy, a cleft lip adhesion can be performed as an initial stage in the repair. The preliminary cleft lip adhesion unites the upper lip and nasal sill, truly converting complete clefts into incomplete clefts. A cleft lip adhesion is performed in the first or second month of life, and the definitive cleft lip and nose repair follows at 4 to 6 months. After the definitive cleft lip and nose repair, the cleft palate is repaired in a single stage at 9 to 12 months of age.

Unilateral Cleft Lip. The unilateral cleft lip is classically associated with a cleft lip nasal deformity. The cleft lip nasal deformity includes lateral, inferior, and posterior displacement of the alar cartilage. This results from the deficient and clefted underlying skeleton as well as the unopposed pull of the clefted orbicularis



A



B



C

Figure 45-12. A. Unilateral cleft lip and palate. B. Bilateral cleft lip and palate. C. Incomplete unilateral cleft lip.

oris muscle abnormally inserted on the alar base (Fig. 45-14A). The maxillary minor segment (the smaller alveolar/maxillary segment on the clefted side) is collapsed medially. The process of unilateral cleft lip repair can be thought of as "philtral subunit reconstruction." The goal of the operation is to level Cupid's bow and reconstruct the central philtrum of the lip, ideally placing the incision and subsequent scar as close to the normal philtral



A



C



B

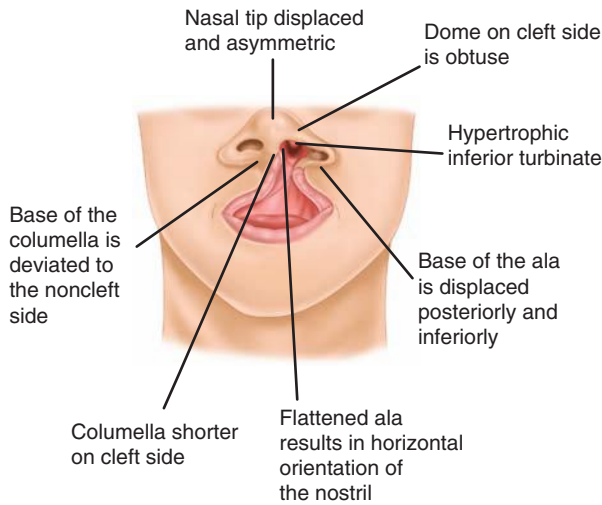


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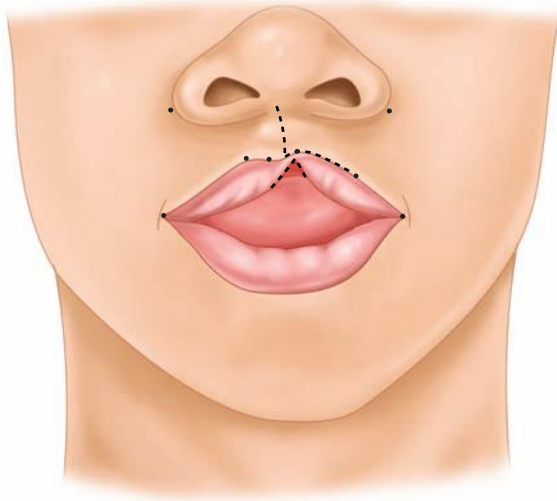


E

Figure 45-13. A. Complete left-sided cleft lip, nose, and palate. B. Nasoalveolar molding. C. After nasoalveolar molding, preoperative appearance before cleft lip and nose repair. D. Frontal view after cleft lip and nose repair. E. Worm's-eye view after cleft lip and nose repair.



A



B

Figure 45-14. A. Unilateral cleft lip and nose deformity. B. The rotation-advancement repair.

column as possible. The surgical repair is performed under general anesthesia, and local anesthesia containing epinephrine is used. Many different techniques of cleft lip and nose repair have been proposed; however, most of the commonly used procedures are variations of a “rotation-advancement” procedure.²¹ The rotation-advancement procedure, as championed by Millard (Fig. 45-14B), rotates the philtral subunit of the central lip downward to level Cupid’s bow as the lateral lip element is advanced into the defect created by the downward rotation of the philtrum. Some surgeons choose to perform primary closure of the alveolar cleft at the time of primary lip and nose repair, called a *gingivoperiosteoplasty*. If the alveolar cleft is to be repaired, the gingivoperiosteoplasty is performed by raising mucoperiosteal flaps within the alveolar cleft margin and reapproximating them across the alveolar cleft defect. This creates a bony tunnel closed with periosteal flaps and facilitates the generation of bone in the alveolar defect. It is accepted today that some form of primary nasoplasty should be performed at the time of primary definitive lip repair. Techniques to release and reposition the nasal tip cartilages, as well as the ala, are performed with variations of tip rhinoplasties using suture methods. Some surgeons choose to use postoperative internal and/or external splints to maintain the nasal correction achieved at surgery during the healing process.

Bilateral Cleft Lip. In the complete bilateral cleft lip and nose deformity, the central lip element, called the *prolabium*, is entirely separate from the rest of the upper lip. The probabium is displaced on top of the central alveolar segment, called the *premaxilla*, containing the unerupted four central incisors. Often, the premaxilla and probabium are outwardly displaced. This is referred to as a *flyaway premaxilla*. For the child with a complete bilateral cleft lip and nose, PSIO is a very important step in preparing the child for definitive lip and nose surgery by retracting the premaxilla into the maxillary arch, repositioning the lip segments, and stretching the rudimentary columella. Bilateral cleft lip and nose repairs often are versions of straight-line repairs, with the Mulliken technique being the more commonly performed (Fig. 45-15). In the bilateral cleft lip deformity, the new philtrum is made from the probabium and is united to the lateral lip elements on top of the repaired orbicularis oris muscle.²²

Cleft Palate. During the eighth to twelfth weeks of gestation, the mandible becomes more prognathic, the tongue drops from beneath the clefted lateral palatine processes, and the palatal

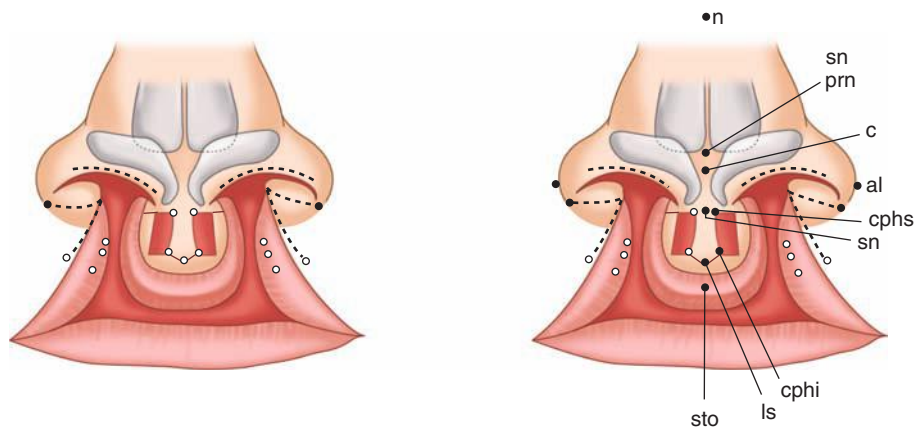


Figure 45-15. Mulliken bilateral cleft lip and nose repair. al = ala nasi; c = highest point of columella nasi; cphi = crista philtri inferior; cphi = crista philtri superior; ls = labiale superius; n = nasion; prn = pronasale; sn = subnasale; sto = stomion.

shelves migrate upward into a more horizontal position and fusion occurs. A cleft palate results from the failure of fusion of the two palatal processes. As with labial clefting, isolated clefts of the palate are multifactorial in etiology, and isolated clefts of the palate are more likely to be associated with other anomalies. Between 8% and 10% of isolated clefts of the palate are associated with the 22q deletion of velocardiofacial syndrome.²³

The main goal of cleft palate surgery is to help the patient attain normal speech, which results from velopharyngeal competence. During speech, the soft palate, or velum, is moved posteriorly and superiorly, primarily by the levator palatini muscle sling that suspends the velum from the skull base. Velopharyngeal competence is obtained during attempted speech when the velum approximates the posterior pharyngeal wall, preventing air and liquid from regurgitating into the nasal cavity. Velopharyngeal competence allows intraoral pressure to be built up for speech sounds. A cleft palate precludes this from occurring and results in velopharyngeal incompetence (VPI). Because it is impossible for the oral and nasal cavities to be partitioned in the patient with a cleft palate, it is also difficult for the patient to develop negative intraoral pressure for an effective suck. Therefore, specialized nurses are used to dispense liquid into the infant's mouth during the suckling motions. Children with clefts of the palate have an increased incidence of otitis media; this may be related to the abnormality of the velar musculature and ineffective function of the eustachian tube. The increased incidence of otitis media can result in hearing loss if not treated appropriately. In addition, VPI and nasal air escape during speech results in hypernasal speech.

As with the repair of cleft lip and nose, the timing, technique, and protocols for cleft palate repair are controversial. Most agree that palate repair should be performed before the development of speech. The cleft palate usually is repaired when the infant is between 6 and 18 months of age. Cleft palate repair also is performed under general anesthesia, with the head slightly hyperextended and a retractor, such as the Dingman mouth gag, placed intraorally to retract the tongue and endotracheal tube. An epinephrine solution is injected into the palate. Techniques of hard palate closure include the use of unipedicled hard palate mucoperiosteal flaps as in the Wardill-Veau-Kilner repair or bipedicled hard palate mucoperiosteal flaps as in the von Langenbeck repair. Both the unipedicled and bipedicled hard palate palatoplasty techniques rely on the greater palatine neurovascular pedicle. Soft palate or velar closure techniques are divided into straight-line and Z-plasty procedures. With either a straight-line or Z-plasty velar repair, the levator palatini muscle should be independently repaired; this is called an *intravelar veloplasty*. The clefted levator is identified coursing sagittally in an anterior-posterior direction, abnormally inserted onto the posterior edge of the hard palate. In intravelar veloplasty, it is released from the posterior edge of the hard palate in the midline and dissected free from abnormal attachments to the aponeurosis of the tensor veli palatini muscle and superior constrictor laterally. After its complete release, the levator palatini muscle is united in the midline, with reconstruction of the levator muscle sling that suspends the velum from the skull base and aids in velopharyngeal competence.

The authors prefer the double opposing Z-plasty technique of soft palate or velar reconstruction known as the *Furlow palatoplasty*.²⁴ The procedure uses four triangular flaps, two oral and two nasal, with the posteriorly based flaps containing the released levator muscles. The Z-plasty lengthens the soft palate, prevents longitudinal scarring from a straight-line repair, and

produces a secondary pharyngoplasty effect by narrowing the velopharyngeal port (Fig. 45-16).

Complications of palatoplasty include wound healing problems resulting in a breakdown of the suture line and the development of a fistula. The literature reports fistula rates ranging from approximately 1% to 20%. Treatment of palatal fistulae is particularly challenging, because the recurrence rates have been noted to approach 96%. The second most common complication of palatoplasty is the incomplete correction of speech and the development of postoperative VPI. The literature reports postoperative VPI rates ranging from 10% to 40%. Some of the best rates of velopharyngeal competence have been reported with the Furlow double opposing Z-plasty palatoplasty. Postoperative VPI is treated with pharyngoplasty—either a posterior pharyngeal flap pharyngoplasty or a sphincter pharyngoplasty. A posterior pharyngeal flap is a static flap formed from the posterior pharyngeal wall including mucosa and a portion of the superior constrictor muscle. The midline superiorly based pharyngeal flap is inset into the posterior free edge of the soft palate, permanently attaching it to the posterior pharyngeal wall. The sphincter pharyngoplasty has been reported to involve creation of a dynamic sphincter made with the bilateral posterior tonsillar pillars containing the palatopharyngeus muscle. The superiorly based tonsillar pillars are elevated from the lateral pharynx and inset into a horizontal incision on the posterior pharyngeal wall at the level of the adenoid pad.

Craniofacial Anomalies

History, Overview, and Classification System. Craniofacial surgery is the subspecialty of plastic surgery dealing with hard and soft tissue deformities of the craniofacial skeleton, treating the congenital, developmental, and acquired defects of the cranial and/or facial skeleton. Craniofacial surgery addresses the functional and equally important appearance-related issues surrounding these deformities. Attempting to separate the functional impairment from the appearance-related issues is arbitrary, because it can be argued that the most important function of a face is to look like a face.²⁵ Numerous studies have established the importance of facial form and the significant emotional impact that facial deformities have on a person's life and sense of self.

The field of craniofacial surgery finds its origins in the aftermath of the world wars and the need to treat massive facial injuries. In 1967, Dr. Paul Tessier, now recognized as the father of craniofacial surgery, first publicly presented his concepts of using wide exposure and a transcranial route to treating craniofacial deformities with large segmental movements of bone. An American disciple of Dr. Tessier, Dr. Linton Whitaker of the Children's Hospital of Philadelphia, working with the Committee on Nomenclature and Classification of Craniofacial Anomalies of the American Cleft Palate-Craniofacial Association, presented a simple and practical classification system for craniofacial anomalies (Table 45-10).

It is the standard of care today that an interdisciplinary team of experts with specialized knowledge and training in treating children with craniofacial anomalies care for children who have such anomalies. The preoperative workup and evaluation must be thorough and should include imaging (computed tomography [CT], magnetic resonance imaging [MRI], and cephalography), photography, blood work, anesthesia consultation, and other components as the condition dictates. Craniofacial procedures are often long, complicated surgeries of significant magnitude, with an attendant risk of blood loss, serious morbidity, and even mortality. Significant blood loss is a realistic possibility, and

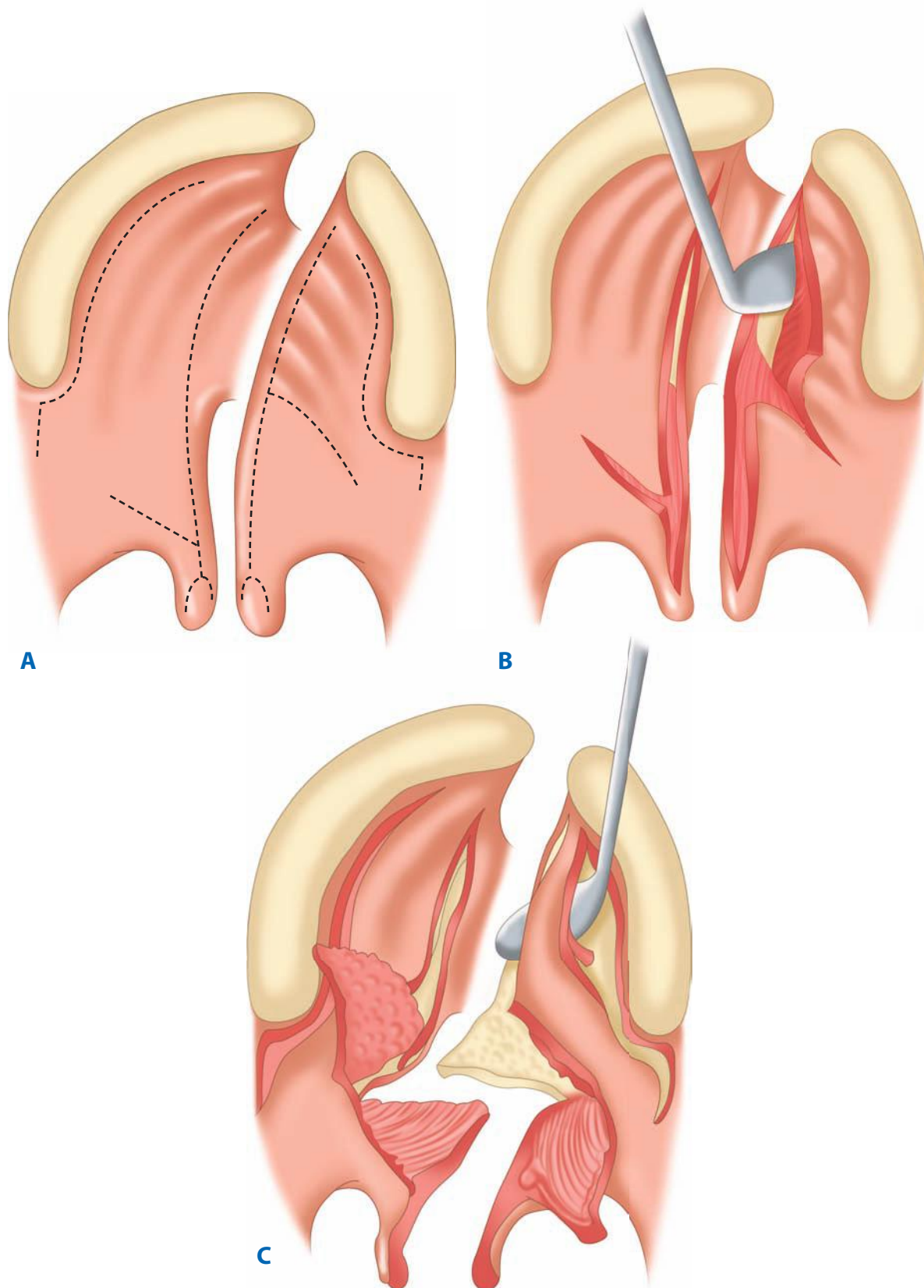


Figure 45-16. A. Markings for the Furlow double opposing Z-plasty palatoplasty. B. Raising the oral flaps in a Furlow palatoplasty. C. The complete dissection of a Furlow palatoplasty.

Table 45-10

Classification of craniofacial anomalies

- I. Clefts
 - a. Centric
 - b. Acentric
- II. Synostoses
 - a. Symmetric
 - b. Asymmetric
- III. Atrophy, hypoplasia
- IV. Neoplasia, hypertrophy, hyperplasia
- V. Unclassified

preparation for blood conservation and transfusion must be made. The routine surgical approach to the craniofacial skeleton can be via a coronal incision, and after a bifrontal craniotomy, the orbital and facial skeleton can be addressed. Bone grafts for reconstruction can be split calvarial grafts or, alternatively, grafts from the ribs or iliac crest. Rigid fixation is obtained with bioresorbable plates, screws, and sutures. Despite the magnitude of the procedures, significant morbidity (e.g., blindness, brain injury, significant infection, cerebrospinal fluid leak, intracranial hematoma) or mortality is rare.

Craniofacial Clefts. The rare craniofacial clefts have been subclassified by Tessier (Fig. 45-17). The Tessier classification

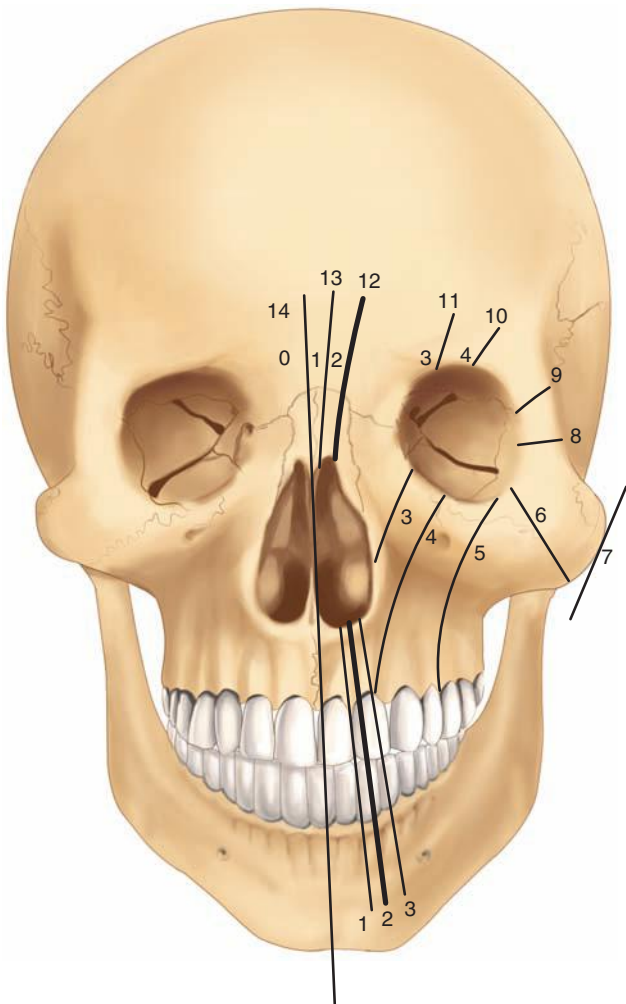
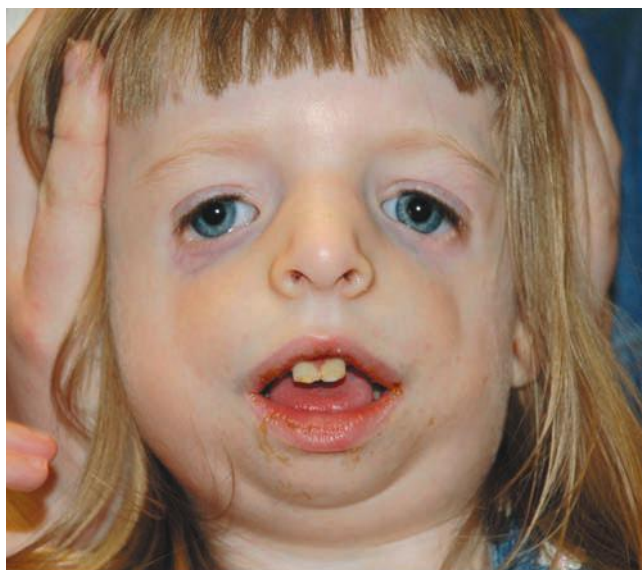


Figure 45-17. Tessier's classification of craniofacial clefts.



Figure 45-18. Craniofacial cleft. (Reproduced with permission from Losee J, Kirschner R, eds. *Comprehensive Cleft Care*. 1st ed. New York: McGraw-Hill Professional; 2008, Chap. 27, Fig. 3. Copyright © The McGraw-Hill Companies, Inc.)

of craniofacial clefts considers the orbit as the center around which the clefts radiate as the spokes of a wheel, numbered from 0 to 14. The facial clefts (0 to 7) and their cranial extensions (8 to 14) are often associated and total 14 (Fig. 45-18). Treacher Collins syndrome (Fig. 45-19), also known as *mandibulofacial dysostosis*, is a type of craniofacial clefting disorder representing bilateral 6-7-8 clefts. This autosomal dominant disorder with variable penetrance has the following manifestations: hypoplasia of the zygomas, asymmetry and hypoplasia of the mandible, ear anomalies, and colobomas of the lower eyelids. Craniofacial microsomia, also known as *hemifacial microsomia*, can be classified as a form of clefting as well (Fig. 45-20). Manifestations of this anomaly usually involve the hard and soft tissue of one half of the craniofacial skeleton. Deformities range in severity from complete absence of an affected facial component (globe, mandible, ear) to mild asymmetries. Ear deformities range from complete absence of the ear to only preauricular skin tags. Similarly, the eye deformities range from complete absence of the globe to various anomalies including epibulbar dermoids. Hypoplasia of the temporal skull, maxilla and zygoma, and orbit are seen in varying degree and affect the underlying skeleton as well as the overlying soft tissues. The classical deformity of hemifacial microsomia affects the mandible. Hypoplasia of the hemimandible, as well as the maxilla, results in dental malocclusions (Fig. 45-20C). Mandibular hypoplasia may range from



A



B



C

Figure 45-19. Child with Treacher Collins syndrome. **A.** Frontal view. **B.** Lateral view. **C.** Three-dimensional computed tomographic scan of the craniofacial skeleton.

minor underdevelopment of otherwise normal components to complete absence of the condyle, ramus, and proximal body.

Treatment of hemifacial microsomia includes management of the airway and attention to other functional conditions. Treatment of the mandibular deformity includes distraction osteogenesis during growth and orthognathic procedures at skeletal maturity. Ear deformities are reconstructed with techniques using costal cartilage and local soft tissue. Soft tissue

deficiencies of the hemiface can be treated with fat injections, dermal-fat grafts, or free tissue transfer. Orbital hypertelorism is yet another type of midline craniofacial (0-14) clefting. *Orbital hypertelorism* is defined as a lateralization of the entire orbit, increasing the intraorbital distance and resulting from midline conditions such as encephaloceles, frontonasal dysplasia, and syndromic craniosynostosis. The treatment of severe orbital hypertelorism includes a transcranial approach to four-wall



A



B



C

Figure 45-20. Child with left-sided craniofacial/hemifacial microsomia. **A.** Frontal view. **B.** Lateral view. **C.** Bite plane.

orbital box osteotomies, resection or treatment of the abnormal midline process, mobilization, medialization of the orbital complexes, and nasal reconstruction with a cantilever nasal bone graft.

Craniosynostosis. The craniosynostoses are a group of disorders that result from the abnormal obliteration or premature fusion of the cranial sutures. The craniosynostoses can be subdivided into simple or single-suture craniosynostoses, and complex, syndromic, or multiple-suture craniosynostoses. The cranial sutures allow for the normal growth of the skull, and therefore, the classic presentation of craniosynostosis is an abnormal head shape. The resultant abnormal head shapes are secondary to an inhibition of skull growth at right angles to the fused suture and a compensatory overexpansion of the skull perpendicular to the fused suture into areas with open sutures. These abnormal head shapes provide a basis for the classification of craniosynostoses. In addition to appearance-related deformities resulting from craniosynostosis, important functional aspects include the potential for intracranial hypertension, which may result from brain growth restricted by an unyielding skull. The chances of intracranial hypertension increase with the number of sutures affected. Blindness and mental deficiencies secondary to an increase in intracranial pressure can likely be prevented by the surgical expansion of the cranium to release the fused suture, correct the abnormal head shape, and remodel the skull. The standard procedure used today in the correction of these synostotic deformities is fronto-orbital advancement. Fronto-orbital advancement, performed using a transcranial approach, includes a frontal craniotomy and orbital repositioning. The complex or multisutural synostoses are often syndromic, resulting from gain-of-function mutations of the fibroblast growth factor receptors (*FGFR1*, *FGFR2*, *FGFR3*). These syndromes of craniosynostosis include Apert's, Crouzon's, Pfeiffer's, and Saethre-Chotzen syndromes. The syndromic craniosynostoses not only include bicoronal synostosis but also involve the midface, with resulting exorbitism and midface hypoplasia. Multilevel airway anomalies, obstructive sleep apnea, corneal exposure, intracranial hypertension, feeding difficulties, and severe malocclusion are some of the associated anomalies found in children with syndromic craniosynostoses. In addition to fronto-orbital advancement, facial osteotomies (i.e., Le Fort III craniofacial disjunction) are required to treat the orbital, midfacial, and occlusal deformities.

Atrophy and Hypoplasia. The categories of craniofacial atrophy and hypoplasia encompass many conditions such as Pierre Robin sequence and Romberg's progressive hemifacial atrophy. Pierre Robin sequence is characterized by three pathognomonic findings: microretrognathia, glossoptosis, and respiratory distress. Pierre Robin sequence may or may not be associated with a palatal cleft. It is thought by some to occur secondary to a fixed and flexed fetal head position that inhibits mandibular growth and results in micrognathia. The micrognathia prevents the natural caudal migration of the tongue from between the clefted palatal shelves, and the resulting deformity as described earlier. The functional consequences include intermittent respiratory obstruction and obstructive sleep apnea that may affect feeding, growth, and safety of the airway. Treatment of a child mildly affected with Pierre Robin sequence may include simply positioning the child prone until the child "grows out" of the condition. However, if the child is severely affected and unable to feed adequately or has an unsafe airway, surgical intervention

is required. For decades, tracheotomy was the initial and definitive treatment of choice; however, today many initially attempt a tongue-lip adhesion, treating the glossoptosis and alleviating respiratory obstruction by suturing the tongue tip to the lower lip. The tongue-lip adhesion is taken down at the time of palatoplasty. Should the tongue-lip adhesion not adequately correct the obstruction, then neonatal mandibular distraction can be used to correct the underlying microretrognathia and relieve the obstructive symptoms (Fig. 45-21). Another syndrome of atrophy and hypoplasia is Romberg's progressive hemifacial atrophy, also known as *Parry-Romberg syndrome* (Fig. 45-22). Romberg's disease is a disorder of unknown etiology, beginning in childhood or adolescence, in which hemifacial atrophy of the skin, subcutaneous fat, muscle, bone, and cartilage progresses for a variable period of time before spontaneously ceasing or "burning out" 2 to 10 years after beginning. Most believe treatment should be delayed until at least 1 year after the process of atrophy has ceased. Some hematologists and oncologists have treated the early presentation of Romberg's disease with chemotherapy. After the cessation of atrophy, reconstruction of the craniofacial skeleton and soft tissues may begin with bone and/or cartilage grafts, alloplastic implants, dermal-fat grafts, fat grafting, and possibly free tissue transfers.

Hyperplasia, Hypertrophy, and Neoplasia. The categories of craniofacial hyperplasia, hypertrophy, and neoplasia encompass a wide variety of conditions affecting the craniofacial skeleton. These include vascular anomalies (discussed later in this chapter), neurofibromatosis, hemifacial hypertrophy, and bony conditions such as osteomas and fibrous dysplasia. Fibrous dysplasia can be monostotic, affecting a single location, or polyostotic, affecting more than a single location in the skeleton; it may be associated with skin pigmentation abnormalities and endocrine involvement, and be termed *polyostotic* or *McCune-Albright syndrome*. Treatment of fibrous dysplasia of the craniofacial skeleton includes block resection and reconstruction with bone grafts. If extensive involvement exists and block resection is not possible or feasible, partial resection and contouring of the affected bone is possible, as long as there is the understanding that long-term outcomes and the behavior of the disease are unpredictable.

Vascular Anomalies

Vascular anomalies are vascular birthmarks that all appear similar: flat or raised, in various shades of red and purple.²⁶ For centuries, they have been named by similarly colored food and drink (i.e., strawberry hemangioma, port-wine stain). Today these vascular birthmarks have been biologically classified as either *hemangiomas* or *vascular malformations*. The Greek suffix *-oma* means "swelling" or "tumor" and today connotes a lesion characterized by hyperplasia. Hemangiomas are congenital vascular anomalies that undergo a phase of rapid growth followed by slow regression, based on endothelial cell kinetics. Malformations are abnormal vascular channels lined with quiescent endothelium, usually are seen at birth, never regress, and have the potential to expand. The differential diagnosis of vascular anomalies is routinely made by a detailed accurate history and clinical examination. For deep lesions, radiographic studies may help determine the diagnosis. Biopsy is used if the diagnosis is uncertain or there is concern over the potential of malignancy.

Hemangiomas. The infantile hemangioma is the most common birthmark, affecting 10% to 12% of whites, with a 3:1 to 5:1 predilection for females and an increased incidence in



A



B



C

Figure 45-21. A. Lateral view of a child with Pierre Robin sequence and mandibular microretrognathia. B. Intraoperative photo of a submandibular incision and planning for the placement of a buried mandibular distractor. C. Lateral view of the child after mandibular distraction with slight overcorrection of retrognathia. The distractor is still in place as evident from the activating rod seen exiting the skin retroauricularly.



Figure 45-22. Frontal view of a child with left-sided Romberg's progressive hemifacial atrophy.

preterm infants (23%) (Fig. 45-23). Hemangiomas are solitary in 80% of cases and multiple in 20%. In children with multiple (more than three) cutaneous hemangiomas, abdominal ultrasound is suggested to rule out hemangiomatosis with visceral involvement. Hemangiomas do not cause bleeding disorders; however, more invasive lesions such as kaposiform hemangioendothelioma can result in Kasabach-Merritt syndrome, characterized by platelet trapping and disordered bleeding.

Hemangiomas are usually first noted around 2 weeks of life as a flat pink spot, often confused with a superficial scratch.



Figure 45-23. Hemangioma of the ear and retroauricular region.

Around the second month of life, they enter the *proliferating phase* in which rapid growth is seen caused by plump, rapidly dividing endothelial cells. If the hemangioma is superficial, the skin becomes crimson and raised; if the lesion is deep, a dark blue or purple color is noted with less superficial swelling. Hemangioma growth frequently peaks before the first year, and then the lesions enter the *involuting phase* in which growth is commiserate with the child. The involuting phase is characterized by diminishing endothelial activity and luminal enlargement. The lesion begins to “gray,” losing its intense reddish color and taking on a purple-gray shade with overlying “crepe paper” skin. The involution phase continues until 5 to 10 years of age. Regression of the lesion is then complete. The *involved phase* begins in 50% of children by 5 years of age and in 70% by 7 years. If there was cutaneous ulceration during the proliferative phase, a cutaneous scar may persist, along with the yellow-gray crepe paper-like skin with fibro-fatty deposition. In 50% of children, near-normal skin is restored.

The treatment of hemangiomas is largely observational, with reassurance of parents that regression and involution will occur. Cutaneous ulceration secondary to a proliferating hemangioma occurs in 5% of cases and more frequently with lip or urogenital lesions. Local wound care, topical application of lidocaine for pain, and laser cauterization may be beneficial treatment modalities. Problematic or endangering hemangiomas (i.e., periocular lesions threatening amblyopia, airway lesions, facially disfiguring lesions) occur in 10% of cases. The first-line treatment for problematic hemangiomas is systemic corticosteroid therapy, which is particularly effective (85% response rate). Second-line therapies include interferon and vincristine, each with its own attendant effectiveness and morbidity. Laser therapy has been claimed by some to be effective in the treatment of early hemangiomas; however, there has been no conclusive proof that laser therapy either diminishes lesion bulk or induces involution. Laser therapy has been effective in lightening affected skin. Surgery for hemangiomas in the proliferating phase is largely limited to treatment of problematic lesions (i.e., eyelid lesions threatening amblyopia). Hemangioma surgery usually is reserved for the treatment of secondary deformities and residual fibro-fatty depositions, among other indications.

Vascular Malformations. Vascular malformations are subclassified by vessel type, such as lymphatic, capillary, venous, or arterial, and by rheologic characteristics, such as slow flow and fast flow. Slow-flow lesions include capillary malformations (CMs) and telangiectasias, lymphatic malformations (LMs), and venous malformations (VMs). Fast-flow lesions include arterial malformations (AMs) and arteriovenous malformations (AVMs). In addition, there are combined malformations. One such combined lesion occurs in Klippel-Trénaunay syndrome in which CMs, LMs, and VMs are found and may be associated with soft tissue and skeletal hypertrophy in one or more of the limbs (Fig. 45-24A).

CMs are pink-red macular vascular stains that are present at birth and persist throughout life. These lesions tend to become more verrucous and darker throughout life. CMs are effectively treated with a pulsed-dye laser, and the results often are better with treatment in infancy and young childhood. Laser therapy often is repetitive and prolonged. CMs of the head and neck, historically called *port-wine stains*, may be associated with Sturge-Weber syndrome, which includes vascular involvement of the leptomeninges and ocular pathology (Fig. 45-24B).



A



B



C



D

Figure 45-24. A. Klippel-Trénaunay syndrome, with combined vascular anomaly (capillary malformation, lymphatic malformation, venous malformation) of the leg. B. Sturge-Weber syndrome, with V1 and V2 capillary malformation of the left face. C. Lymphatic malformation of the neck, previously referred to as *cystic hygroma*. D. Venous malformation of the forehead.

LMs are anomalous lymphatic channels that never regress and have the potential to affect underlying muscle and bone, causing significant swelling and bony overgrowth. They have historically been called *lymphangiomas* or *cystic hygromas* (Fig. 45-24C). LMs can be classified as microcystic, macrocystic, or both. LMs expand or contract with the flow of lymph, infection, or intralesional hemorrhage. Superficial LMs that affect the skin often produce cutaneous vesicles that may coalesce and weep lymph fluid. Sclerotherapy remains a major treatment modality for LMs, and lesions that are macrocystic can be aspirated before sclerotherapy. Although surgery rarely removes the entire lesion, surgical resection is the only possibility for cure. These resections often are challenging, lengthy, and associated with significant blood loss, and the potential exists for regeneration of lymph channels and recurrence of the LMs postoperatively.

VMs are frequently bluish, soft, and compressible, and swell when dependent (Fig. 45-24D). VMs grow with the child, expand slowly, and may enlarge during puberty. Patients often complain about stiffness and pain with thrombosis. VMs can affect the skin, muscle, and bone. MRI is the modality of choice for imaging these lesions. Preoperative sclerosis followed by surgical extirpation is the treatment of choice for VMs that cause functional or appearance-related disability. VMs have the tendency to recanalize and re-expand. Use of elastic support stocking and low-dose aspirin therapy are important adjunctive treatment modalities for VMs involving the legs.

Pure AMs are rare and more commonly present as AVMs. AVMs appear as red violaceous skin with a palpable mass beneath. Local warmth, bruit, and thrill are frequently present. AVMs have the likely consequences of ischemic changes, ulceration, intractable pain, and intermittent bleeding. The natural history of AVMs has been described as consisting of four stages: quiescence, expansion, destruction, and decompensation. Usually, treatment for AVM is initiated when signs and symptoms of ischemic pain, ulceration, bleeding, or hemodynamic instability (stages 3 and 4) are evident. Surgical treatment includes arterial embolization to temporarily occlude the nidus 24 to 72 hours before surgical extirpation. The nidus and overlying affected skin must be widely excised, and reconstruction can be performed afterward.

Congenital Melanocytic Nevi

Congenital melanocytic nevi (CMNs) contain nevus cells and are usually present at birth. Lesions are frequently light to dark brown and round or oval, and vary greatly in size, pattern, and anatomic location. The most common location of CMNs is the trunk, followed by the extremities and head and neck. Frequently, larger lesions are associated with multiple smaller satellite lesions. Over time, these lesions may become less (or sometimes more) pigmented and develop hypertrichosis and a variegated texture, including nodularity. Small CMNs are <1.5 cm in diameter, and large ones are >10 cm. Giant CMNs usually are >20 cm in their greatest dimension in adulthood, and this correlates with a 9-cm scalp lesion or a 6-cm trunk lesion in an infant. All CMNs should be monitored for worrisome changes that indicate the need for biopsy, including ulceration, uneven pigmentation, change in shape, and nodularity. There is controversy over the actual incidence of malignant transformation of CMNs; however, most experts believe that melanoma may arise directly from a CMN. No convincing study to date has proven that excision of a CMN reduces

the rate of malignant transformation to melanoma; however, many clinicians feel that excision serves at least to debulk the lesion. The reported lifetime risk for melanoma arising in small or large CMNs is between 0% and 5%; the risk for giant CMNs is estimated to be between 5% and 10%.²⁷ In addition to being at risk for melanoma, patients with large or giant CMNs are at risk for neurocutaneous melanocytosis (leptomeningeal melanosis), and this condition includes collections of melanocytes in the leptomeninges. Neurocutaneous melanocytosis carries a lifetime nonreducible risk of central nervous system melanoma and other morbidity and mortality from seizures, hydrocephalus, and other central nervous system conditions. MRI screening for infants born with large or giant CMNs is recommended to make the diagnosis of neurocutaneous melanocytosis.

Many different treatments have been advocated for the child with CMN; however, the overwhelming goals are to remove (or at least reduce) the risk of malignant transformation, preserve function, and improve cosmesis. Dermabrasion, chemical peels, and laser therapy have been reported to improve the appearance; however, none of these modalities completely removes nevus cells. To address malignant potential, only complete excision is a possible solution, and this is difficult, because nevus cells may extend beyond the skin and into the deep subcutaneous tissue and even the underlying muscle. The surgical options include direct excision and primary closure, serial excision, excision and skin grafting, and staged tissue expansion with subsequent lesion excision and flap reconstruction (Fig. 45-25). Treatment options have particular indications with respect to the location of the nevus. Scalp lesions are best treated with tissue expansion. Full-thickness skin grafting is best used for ear and eyelid reconstruction. Tissue expansion is associated with increased morbidity in lower extremity reconstruction, and therefore excision and grafting, even with previously expanded full-thickness skin grafts, is often the treatment of choice. In summary, CMNs often are treated surgically to decrease the risk of malignant degeneration to melanoma as well as to correct the significant appearance-related deformity.

4► RECONSTRUCTIVE SURGERY

Facial Reconstruction after Fracture

General Principles. As technologic advances raise the level of energy involved in modern systems of transportation, recreation, and weaponry, so follow increases in the degree of maxillofacial destruction related to misadventures with this technology. The first phase of care for the patient with maxillofacial trauma is activation of the advanced trauma life support protocol. Concomitant injuries beyond the face are the rule rather than the exception. The most common life-threatening considerations in the facial trauma patient are airway maintenance, control of bleeding, identification and treatment of aspiration, and identification of other injuries. Once the patient's condition has been stabilized and life-threatening injuries treated, attention is directed to diagnosis and management of craniofacial injuries.

Physical examination of the face with attention to lacerations, bony step-offs, instability, tenderness, ecchymosis, facial asymmetry, and deformity guides the examiner to underlying hard tissue injuries. Traditional specialized radiography has largely been replaced by widely available high-resolution CT. Coronal, sagittal, and three-dimensional reconstructions of images further elucidate complex injuries.



A



B



C

Figure 45-25. A. Congenital melanocytic nevus (CMN) of the posterior shoulder. B. Treatment of CMN of the posterior shoulder with tissue expansion. C. Appearance of the posterior shoulder after removal of tissue expanders, excision of the CMN, and flap coverage.

Mandible Fractures. Mandibular fractures are common injuries that may lead to permanent disability if not diagnosed and properly treated. The mandibular angle, ramus, coronoid process, and condyle are points of attachment for the muscles of mastication, including the masseter, temporalis, lateral pterygoid, and medial pterygoid muscles (Fig. 45-26). Fractures are frequently multiple, and disturbances in dental occlusion reflect the forces of the many muscles of mastication on the fracture segments. Dental occlusion is perhaps the most important basic relationship to understand about fracture of the midface and mandible. The Angle classification system describes the relationship of the maxillary teeth to the mandibular teeth.

Class I is normal occlusion, with the mesial buccal cusp of the first maxillary molar fitting into the intercusp groove of the mandibular first molar. Class II malocclusion is characterized by anterior (mesial) positioning, and class III malocclusion is posterior (distal) positioning of the maxillary teeth with respect to the mandibular teeth (Fig. 45-27).

Nonsurgical treatment may be used in situations in which there is minimal displacement, preservation of the pretraumatic occlusive relationship, and normal range of motion. The goals of surgical treatment include restoration of pretraumatic dental occlusion, reduction and stable fixation of the fracture, and repair of soft tissue. Operative repair involves seating of the

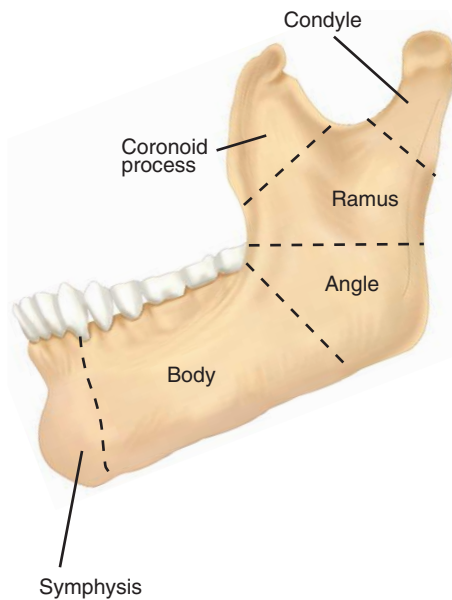


Figure 45-26. Mandibular anatomy. (Reproduced with permission from Thornton J, Hollier L. *Facial fractures II: lower third*. Selected Readings Plast Surg. 2002;9:1.)

condyles within the glenoid fossa, achievement of maxillary-mandibular fixation with arch bars or intermaxillary screws to establish proper dental occlusion, and intraoral, extraoral, or combination surgical exposure of fracture lines. The mandibular plating approach follows one of two schools of thought: rigid fixation as espoused by the Association for Osteosynthesis/Association for the Study of Internal Fixation (AO/ASIF) and less rigid but functionally stable fixation (Champy technique). Regardless of the stabilization approach, one of the

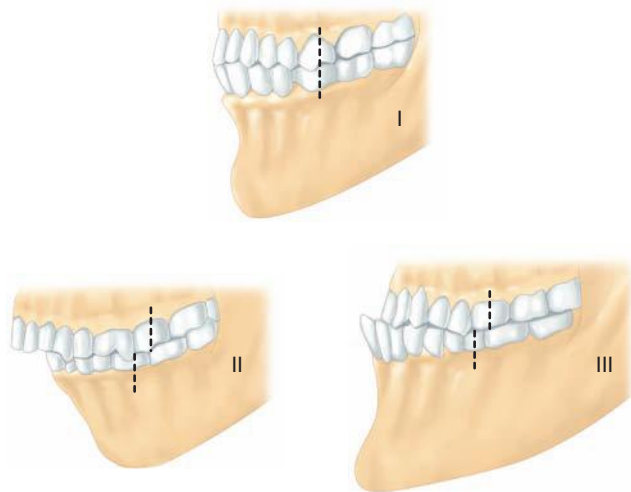


Figure 45-27. Angle classification. Class I: The mesial buccal cusp of the maxillary first molar fits into the intercuspal groove of the mandibular first molar. Class II: The mesial buccal cusp of the maxillary first molar is mesial to the intercuspal groove of the mandibular first molar. Class III: The mesial buccal cusp of the maxillary first molar is distal to the intercuspal groove of the mandibular first molar. (Reproduced with permission from Thornton J, Hollier L. *Facial fractures II: lower third*. Selected Readings Plast Surg. 2002;9:1.)

postoperative objectives is release from maxillary-mandibular fixation and resumption of range of motion as soon as possible to minimize the risk of ankylosis. Other potential complications include infection, nonunion, malunion, malocclusion, facial nerve branch injury, infra-alveolar or mental nerve injury, and dental fractures.

Orbital Fractures. Treatment of all but the simplest orbital injuries should include evaluation by an eye specialist to assess visual acuity and rule out globe injury. Orbital fractures may involve the orbital roof, floor, or lateral or medial walls. The most common orbital fracture is the orbital floor blow-out fracture caused by direct pressure to the globe and sudden increase in intraorbital pressure. Because the medial floor and inferior medial wall are made of the thinnest bone, fractures occur most frequently at these locations. These injuries may be treated expectantly if they are sufficiently small and without complication. However, larger blow-out fractures and those associated with enophthalmos (increased intraorbital volume), entrapment of inferior orbital tissues, or diplopia lasting >2 weeks generally require surgical treatment.²⁸ There are many approaches to the orbital floor, including the transconjunctival, subciliary, and lower blepharoplasty incisions. All provide access to the orbital floor and allow for repair with a multitude of different autogenous and synthetic materials. Late complications include persistent diplopia, enophthalmos, ectropion, and entropion.

Lateral and inferior orbital rim fractures also are not uncommon and are often associated with the zygomaticomaxillary complex fracture pattern, as discussed later.

Special mention should be made of two uncommon complications after orbital fracture. Superior orbital fissure syndrome results from compression of structures contained in the superior orbital fissure in the posterior orbit. These include cranial nerves III, IV, and VI, and the first sensory division of cranial nerve V. Compression of these structures leads to symptoms of eyelid ptosis, globe proptosis, paralysis of the extraocular muscles, and anesthesia in the cranial nerve V1 distribution. If the optic nerve (cranial nerve II) is also involved, symptoms include blindness and the syndrome is dubbed *orbital apex syndrome*. Both of these syndromes are medical emergencies, and steroid therapy and surgical decompression are considered.

Zygoma and Zygomaticomaxillary Complex Fractures.

The zygoma forms the lateral and inferior borders of the orbit. It articulates with the sphenoid bone in the lateral orbit, the maxilla medially and inferiorly, the frontal bone superiorly, and the temporal bone laterally (Fig. 45-28). Zygoma fractures may involve the arch alone or many of its bony relationships. Isolated arch fractures manifest as a flattened, wide face with associated edema and ecchymosis. Nondisplaced fractures may be treated nonsurgically, whereas displaced and comminuted arch fractures may be reduced and stabilized indirectly (Gilles approach) or, for more complicated fractures, directly through a coronal incision.

The zygomaticomaxillary complex (ZMC) fracture involves disruption of the zygomatic arch, the inferior orbital rim buttress, the zygomaticomaxillary buttress, the lateral orbital wall, and the zygomaticofrontal buttress. The fracture segment tends to rotate laterally and inferiorly, creating an expanded orbital volume, limited mandibular excursion, an inferior cant to the palpebral fissure, and a flattened malar eminence. ZMC fractures are almost always accompanied by numbness in the infraorbital nerve distribution and subconjunctival hematoma.

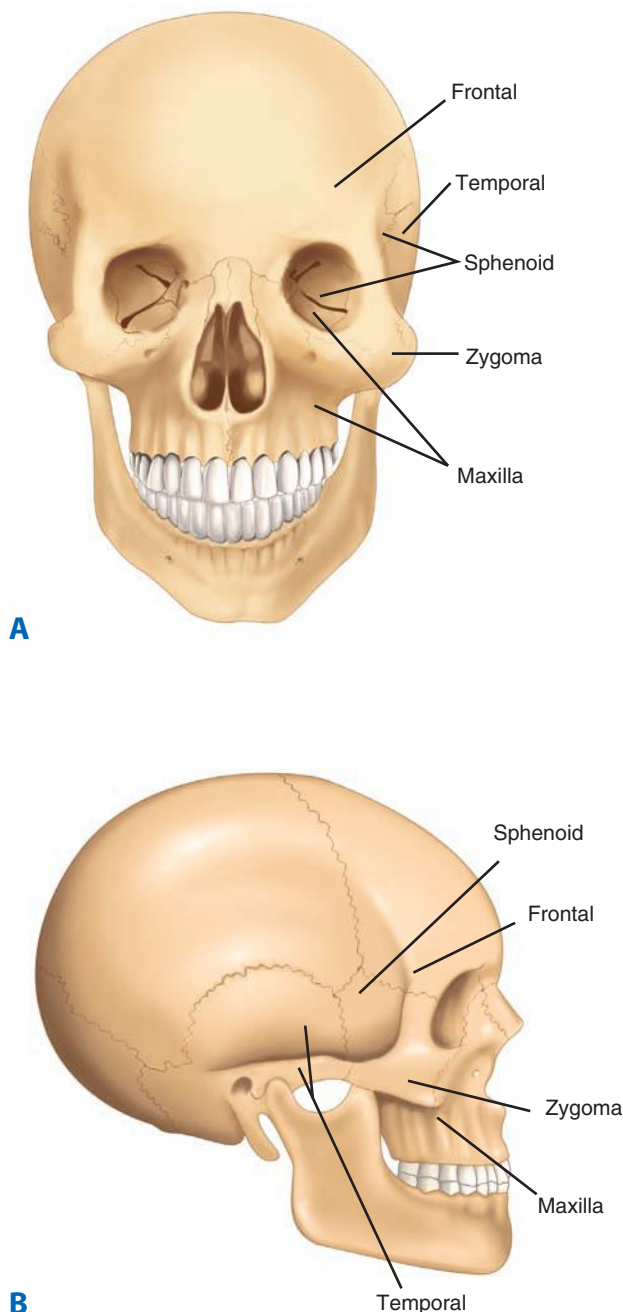


Figure 45-28. Facial bone anatomy. (Reproduced with permission from Hollier and Thornton.²⁸)

Displaced fractures are treated by exposure through multiple incisions to gain access to all of the buttresses requiring fixation. These include the upper eyelid incision (zygomaticofrontal buttress and lateral orbital wall), the subtarsal or transconjunctival incision (orbital floor and infraorbital rim), and the maxillary gingivobuccal sulcus incision (zygomaticomaxillary buttress). Again, significantly complex zygomatic fractures require wide exposure through a coronal approach.⁵

Naso-Orbital-Ethmoid Fractures. Naso-orbital-ethmoid (NOE) fractures are often part of a constellation of panfacial fractures and intracranial injuries. Anatomically, the fracture pattern involves the medial orbits, nasal bones, nasal processes of the frontal bone, and frontal processes of the maxilla. These injuries result in severe functional deficit and cosmetic

deformity from collapse of the nose, ethmoids, and medial orbits; displacement of medial canthal ligament fixation; and nasolacrimal apparatus disruption. Telecanthus is produced by splaying apart of the nasomaxillary buttresses to which the medial canthal ligaments are attached. Treatment typically involves plating or wiring all bone fragments meticulously, potentially with primary bone grafting, to restore their normal configuration. Key to the successful repair of an NOE fracture is the careful re-establishment of the nasomaxillary buttress and restoration of the pretrauma fixation points of the medial canthal ligaments. If comminution is severe, this may be achievable using transnasal wiring of the ligaments.

Frontal Sinus Fractures. The region of the frontal sinus is a relatively weak structural point in the upper face. For this reason, it is a common location for fracture in facial trauma. The paired sinuses each have an anterior bony table that determines the contour of the forehead and a posterior table that separates the sinus from the dura. Each sinus drains through the medial floor into its frontonasal duct, which empties into the middle meatus within the nose. Treatment of a frontal sinus fracture depends on the fracture characteristics (Fig. 45-29).

Nasal Fractures. The nose is the most common facial fracture site due to its prominent location, and such fracture can involve the cartilaginous nasal septum, the nasal bones, or both. It is important to perform an intranasal examination to determine whether a septal hematoma is present. If present, a septal hematoma must be incised, drained, and packed to prevent pressure necrosis of the nasal septum and long-term midvault collapse. Closed reduction of nasal fractures may be performed under local or general anesthesia. Unfortunately, many, if not most, show some deformity upon final healing, requiring rhinoplasty if airway obstruction is present or if improved appearance is desired.

Panfacial Fractures. Fractures of multiple bones in various locations fall into the category of panfacial fracture. These may involve frontal and maxillary sinus fractures, NOE fractures, orbital and ZMC fractures, palatal fractures, and complex mandible fractures. The difficulty in the repair of these injuries lies not in the technical aspects of fixation but in the reestablishment of normal relationships between facial features in the absence of all pretraumatic reference points. Without proper correction of bony fragment relationships, facial width is exaggerated and facial projection is lost. The key point in approaching the patient with a panfacial fracture is first to reduce and repair the zygomatic arches and frontal bar to establish the frame and width of the face. The nasomaxillary and zygomaticomaxillary buttresses may then be repaired within this correct frame. Next, the maxilla may be reduced to this framework, followed by palatal fixation if needed. Finally, now that the midface relationships have been corrected, maxillary-mandibular fixation can be applied with the mandible in correct occlusion followed by plating of any mandibular fractures.²⁹

Ear Reconstruction

Acquired defects of the auricle have many causes, and many different choices for reconstruction are available. Reconstructive approach often is determined by the size and location of the defect. Small helical lesions may be simply excised as a wedge and closed primarily. Larger defects of the upper and middle thirds of the ear may use antihelical and conchal cartilage reduction patterns to reduce the circumference of the helix to allow

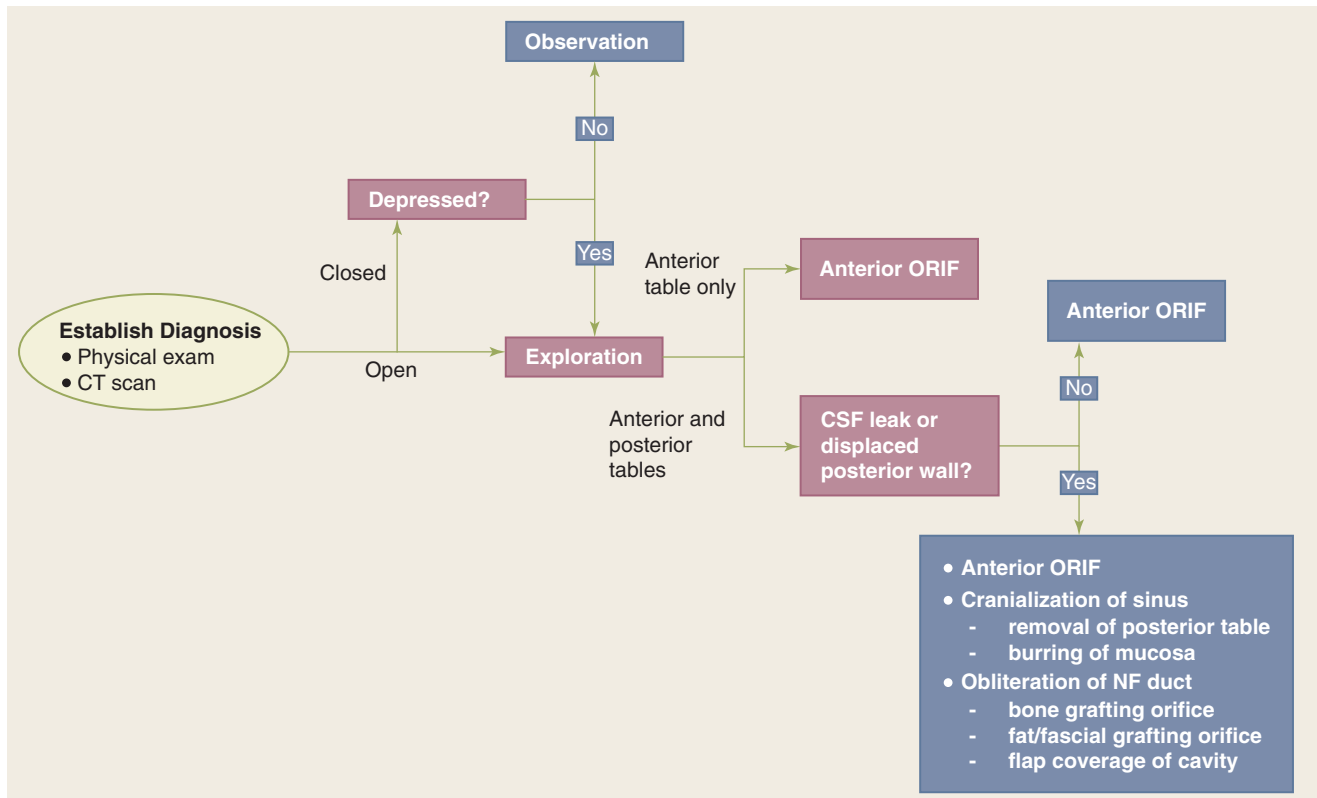


Figure 45-29. Algorithm for the treatment of frontal sinus fracture. CSF = cerebrospinal fluid; CT = computed tomography; NF = nasofrontal; ORIF = open reduction, internal fixation.

primary closure. When helical defects are too large for this solution, local flaps may be used to close or re-create the missing tissue. Postauricular flaps created in staged procedures may be manipulated to create a skin tube mimicking the furled helix and bridging the gap of a defect. Alternatively, use of an Antia-Buch chondrocutaneous advancement flap combined with cartilaginous reduction allows for closure of defects³⁰ (Fig. 45-30). Even larger defects of the upper and middle thirds of the ear may be reconstructed with large local skin flaps combined with contralateral cartilage grafts or contralateral composite grafts. Although ear lobe defects are relatively simple to close primarily, lower third auricular defects that involve more than just the lobe are complex and require cartilaginous support, often combined with local skin flaps.

Nasal Reconstruction

Reconstruction of the nose requires appreciation of the nine aesthetic subunits that are defined by normal anatomic contours and lighting patterns (Fig. 45-31). In general, if a defect involves $\geq 50\%$ of a subunit, the remainder of the subunit should be excised and included in the reconstruction. The nose can be thought of as being composed of three layers: skin cover, structural support, and mucosal lining. When a defect or anticipated defect is evaluated, it is useful to consider what layers of tissue will be missing so that a reconstruction can be devised that replaces each layer. Healing by secondary intention is successfully used in concavities such as the alar groove. Split- or full-thickness skin grafts may be used for superficial defects of the nasal dorsum or sidewall. Composite grafts may be used for the nasal tip or alar rim (see Fig. 45-3). Local random pattern flaps are useful in closing small defects of the dorsum and tip and may be combined with cartilage grafts if structural

support is needed. Axial pattern flaps are commonly used for larger defects. These flaps have the advantage of being able to cover and revascularize underlying cartilage grafts and enjoy a close color match to surrounding skin. Workhorse flaps used in nasal reconstruction include the nasolabial flap and the paramedian forehead flap (Fig. 45-32). Even larger defects may require scalping flaps or free radial forearm flaps. Split calvarial cantilever bone grafts may provide the nasal dorsum support. Lining is generally achieved with scar tissue turnover flaps, mucoperichondrial flaps from within the nasal vestibule, or skin grafting of the underside of transposed flaps.

Lip Reconstruction

The lips are important for articulate speech, eating, maintenance of oral competence, facial expression, and aesthetic harmony of the lower face. Three layers of tissue form the upper and lower lips: skin, muscle, and mucosa. Blood supply is through the facial artery and its branches to the lip, the superior and inferior labial arteries. Lip defects can arise from trauma, burns, neoplasms, congenital lesions, clefts, or infection. As with almost all types of reconstruction, choice of technique is heavily dependent on defect size, location, and deficient structures. The goals of lip reconstruction are restoration of the competent oral sphincter with vermilion apposition, preservation of sensation, and avoidance of microstomia, all while preserving a near-normal static and dynamic appearance. In the upper and lower lip, vermilion-only defects can be corrected with advancement of the labial mucosa, often called a *lip shave*. In defects of less than one-third the horizontal length, enough redundancy is present to allow primary closure. More complex decisions must be made for defects that are between one-third and two-thirds of the total lip length.

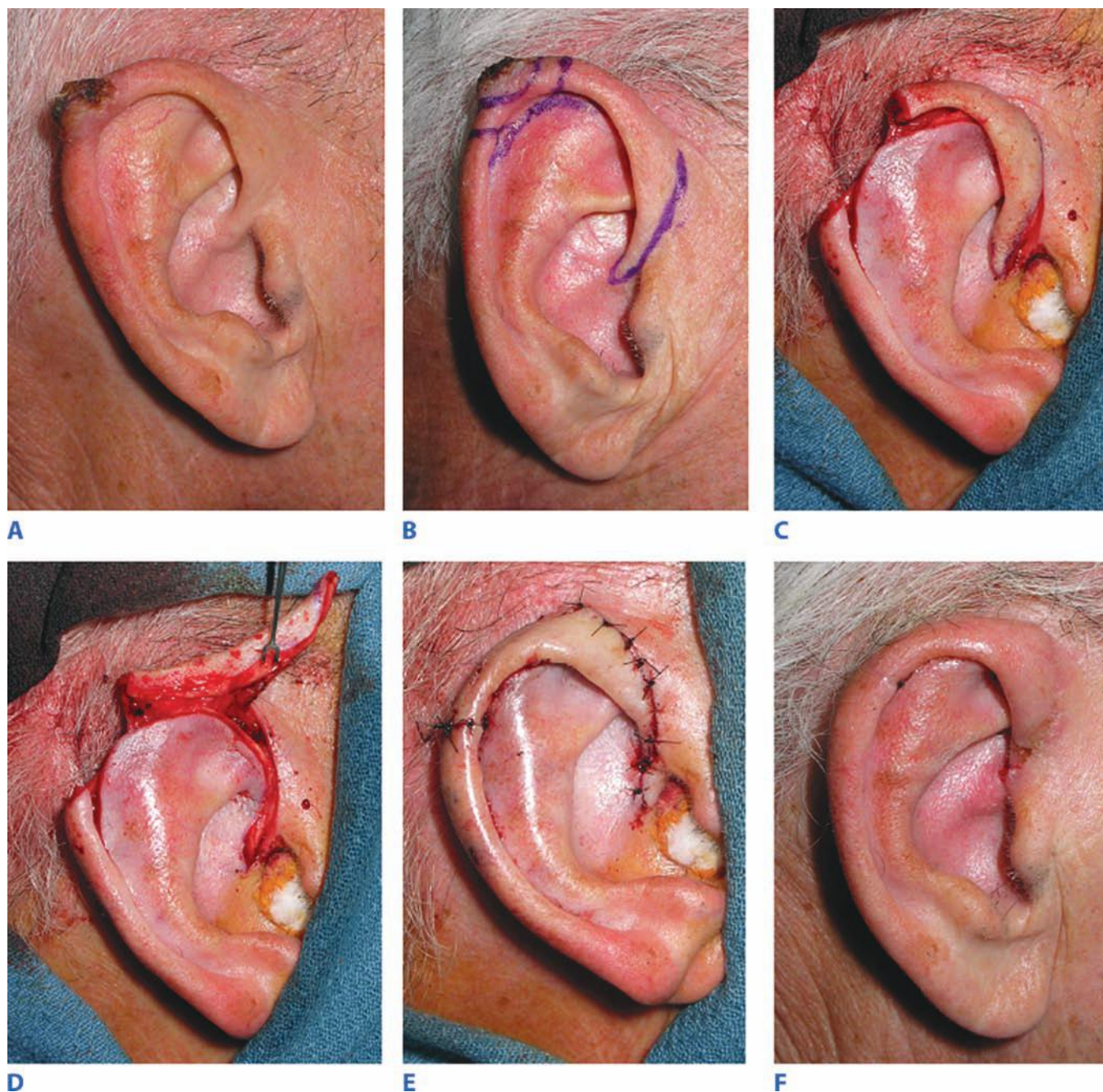


Figure 45-30. Modified Antia-Buch ear reconstruction. **A.** Superior helix lesion. **B.** Excision pattern and reconstruction markings. **C.** Defect, flap elevation, and cartilage reduction. **D.** V-Y advancement of the flap. **E.** Flap inseting. **F.** Appearance at 1 month after surgery. (Photographs reproduced with permission from M. Gimbel.)

The two categories of lip flap technique are transoral cross-lip flaps and circumoral advancements flaps. Cross-lip flaps include the Abbé flap and the Estlander flap. The Abbé flap was originally designed to reconstruct central upper lip (tubercle) defects with lower lip full-thickness tissue vascularized by one of the labial arteries (Fig. 45-33). The technique requires a second-stage procedure for division of the pedicle. The Estlander flap is similar in principle but is based laterally at the oral commissure and is used to reconstruct lateral upper or lower lip lesions. Both the Estlander and Abbé flaps are denervated, but sensation and perhaps even motor function return over months.³¹ The Karapandzic technique is an advancement-rotation flap technique designed for central lower lip defects.

Although good function, sensation, and mobility are preserved, a side effect is reduction in the size of the oral aperture. The Webster-Bernard technique uses cheek tissue advancement flaps to replace defects with full-thickness or partial-thickness cheek incisions extended laterally from the commissure (Fig. 45-34). When performed bilaterally, both the Karapandzic and the Webster-Bernard methods can be used to reconstruct a complete upper or lower lip.

In addition, microvascular free tissue transfer reconstruction may be necessary in cases where there is no remaining lip. The radial forearm free flap is the most commonly used for this purpose, usually transferred with the palmaris longus tendon for lip support.

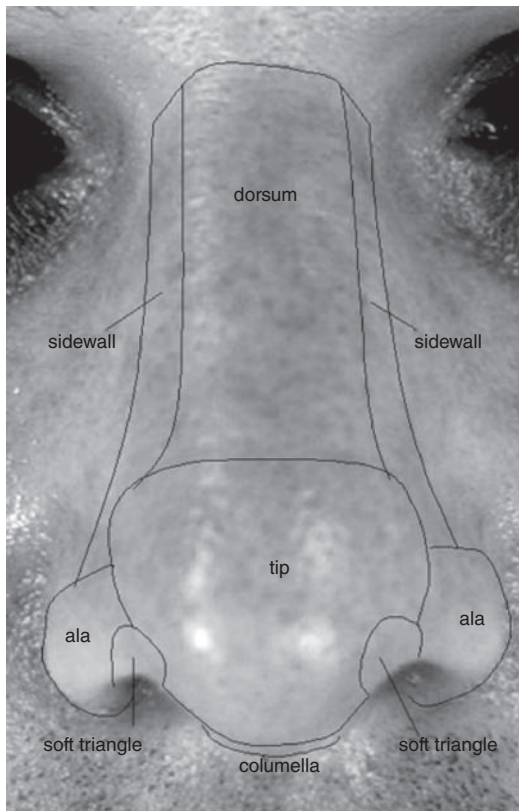


Figure 45-31. Nasal aesthetic subunits. (Photograph reproduced with permission from M. Gimbel.)

Eyelid Reconstruction

The eyelids protect the eye from exposure and are another crucial aesthetic structure of the face. They consist of an anterior lamella (skin and orbicularis oculi muscle) and a posterior lamella (tarsus and conjunctiva). The eyelid blood supply is robust, and ischemia is rarely a concern in reconstruction.

Upper Eyelid. Defects comprising <25% of the upper eyelid can generally be closed primarily in pentagonal approximating fashion (Fig. 45-35). For defects involving 25% to 50% of the upper eyelid, lateral canthotomy (release of the lateral canthal tendon) and cantholysis (release of the superior limb of the lateral palpebral tendon) can be performed to allow advancement and are often combined with use of a lateral semicircular flap (Fig. 45-36). Defects larger than 50% of the upper eyelid may be reconstructed with a Cutler-Beard full-thickness advancement flap or a modified Hughes tarsoconjunctival advancement flap (Fig. 45-37).

Lower Eyelid. Lower eyelid reconstruction considerations parallel those for the upper eyelid. In addition, special attention must be given to the prevention of scleral visibility and ectropion, which can arise from excessive vertical tension due to either technique or scarring. Similar reconstructive methods may be used, including direct closure, semicircular flaps and canthal release, and advancement flaps. Grafts may also be used if the defect is partial thickness. Full-thickness contralateral upper eyelid skin grafts are suitable for replacing the anterior lamella. The posterior lamella requires sturdy, nonkeratinized graft tissue, such as cartilage (tarsal, ear, or



Figure 45-32. Nasal reconstruction with axial pattern flaps. *Top row:* Nasolabial flap reconstruction of an alar defect. *Bottom row:* Paramedian forehead flap reconstruction of the nasal lobule. (Photographs reproduced with permission from M. Gimbel.)

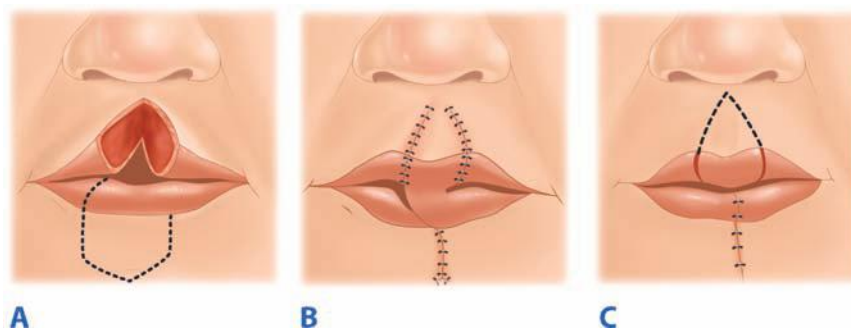


Figure 45-33. Abbé flap upper lip reconstruction. **A.** Defect and flap design. **B.** Rotation of the flap and primary closure of the donor site. **C.** Division of the pedicle (after 2 to 3 weeks) and final inseting.

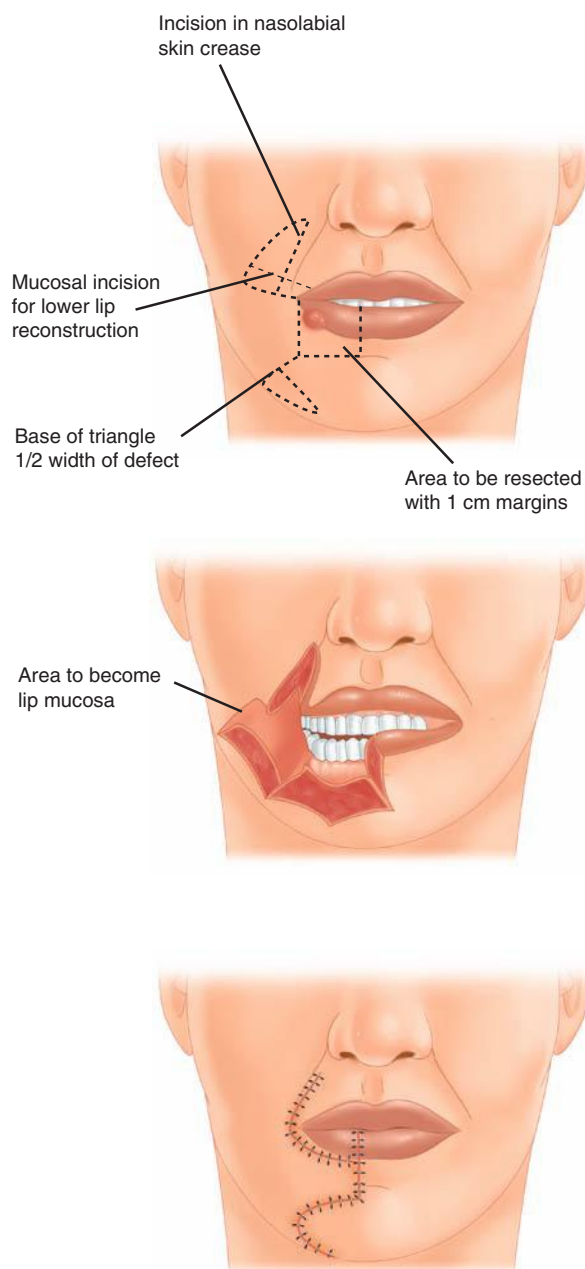


Figure 45-34. Webster-Bernard lip reconstruction technique. (Reproduced with permission from Clossmann JJ, Pogrel A, Schmidt BL. Reconstruction of perioral defects following resection for oral squamous cell carcinoma. *J Oral Maxillofac Surg.* 2006;64:367. Copyright Elsevier.)

nasal septal) or hard palate mucosal grafts, to allow globe apposition.³²

Ptosis. In the normal eyelid, the orbicularis oculi muscle, Müller's muscle, and levator palpebrae muscle act in concert to open and close the palpebral aperture and to maintain the level of the upper eyelid with respect to the pupil. Eyelid ptosis is created by derangement of this cooperative action. Ptosis may be congenital or acquired. Congenital ptosis is caused by lid anomalies, ophthalmoplegia, and synkinesis, whereas acquired ptosis can be neurogenic, myogenic, or traumatic in nature. Horner's syndrome is a form of neurogenic ptosis caused by interrupted sympathetic innervation that leads to ptosis, miosis, and anhidrosis. A thorough evaluation of the ptotic patient includes a general eye and visual acuity examination, attention to signs of exposure or irritation, measurement of marginal-reflex distance, observation of the height of the supratarsal fold, and assessment of levator function. Severity of ptosis and degree of levator dysfunction are critical in deciding the appropriate corrective procedure (Table 45-11). Mild ptosis may be addressed with the Fasanella-Servat procedure, which involves excision of the superior tarsal edge, conjunctiva, and levator aponeurosis, and mullerectomy. Other corrections of mild ptosis usually involve variations on this procedure. Moderate ptosis with fair to good levator function may be treated with some form of a levator aponeurosis shortening procedure. Severe ptosis with poor levator

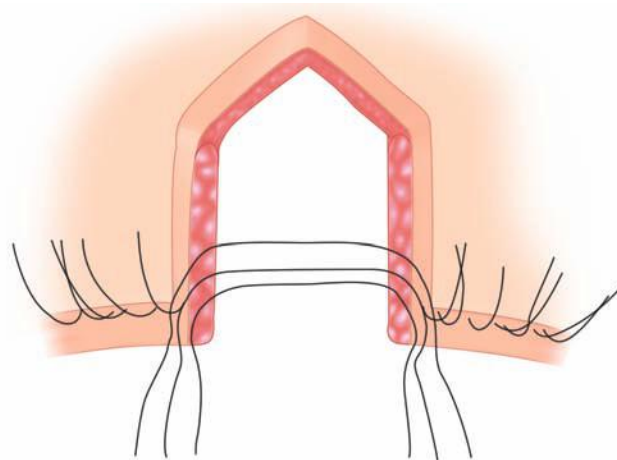


Figure 45-35. Upper eyelid defect of <25%. Primary closure. (Reproduced with permission from Pham RT. Reconstruction of the upper eyelid. *Otolaryngol Clin North Am.* 2005;38:1023. Copyright Elsevier.)

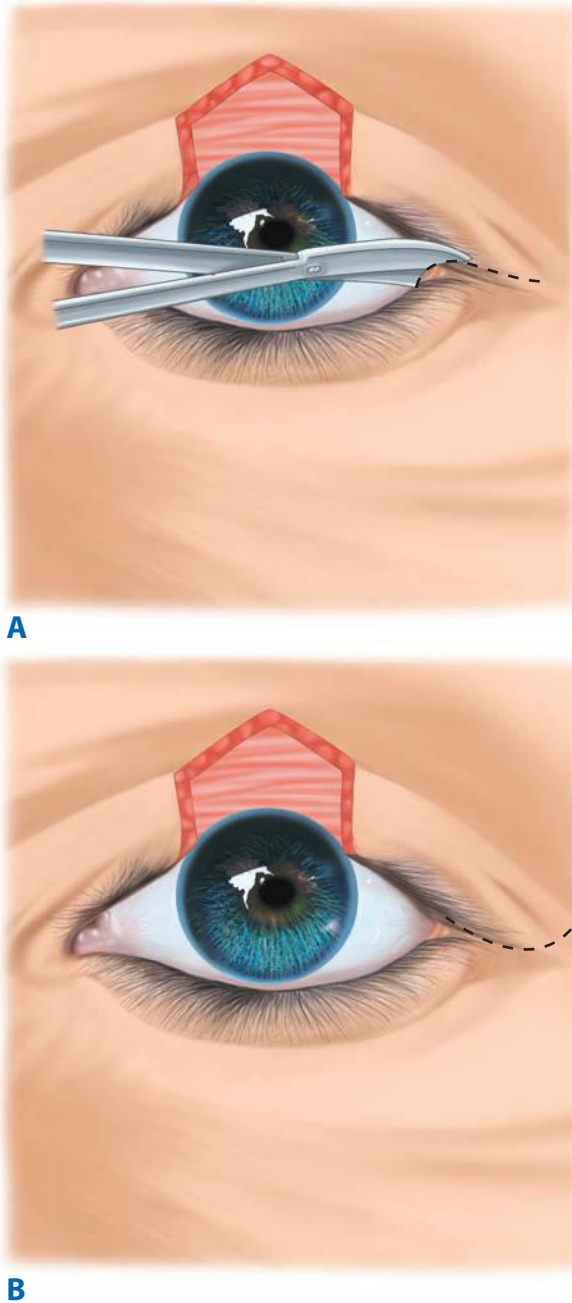


Figure 45-36. Upper eyelid defect of 25% to 50%. **A.** Lateral canthotomy. **B.** Semicircular flap. (Reproduced with permission from Pham RT. *Reconstruction of the upper eyelid*. Otolaryngol Clin North Am. 2005;38:1023. Copyright Elsevier.)

function requires use of an alternate eyelid motor. The frontalis muscle fascial sling technique, which uses strips of fascial grafts sutured to the frontalis muscle, is one such solution.

Skull and Scalp Reconstruction

Scalp Reconstruction. The scalp is formed of five layers: Skin, subCutaneous tissue, galea Aponeurotica, Loose areolar tissue, and Pericranium (SCALP). The scalp is well vascularized bilaterally by branches of the external carotid artery, including the superficial temporal arteries, the occipital arteries, and the posterior auricular arteries. In addition, the bilateral supraorbital and supratrochlear arteries contribute to the

forehead and anterior scalp blood supply. These vessels run in the subcutaneous tissue layer, just superficial to the galea. Because of this rich blood supply, scalp lacerations can lead to dramatic blood loss, an event that usually can be curtailed by a simple running/locking suture closure.

Partial-thickness scalp loss due to trauma usually occurs at the level of the loose areolar tissue plane and is treated initially with débridement of devitalized tissue. If a partial-thickness defect is small enough, primary closure or skin graft can be used. Although the cosmetic result is often less than desirable, all layers of the scalp will accept a skin graft, including the calvaria if it is buried down to its diploë. Because the scalp is relatively inelastic, scoring of the galeal layer often facilitates closure of full-thickness defects, but care must be taken to avoid lacerating the blood vessels just superficial to the galea. Larger areas of loss (4–8 cm) may be covered with large scalp flaps, as classically described by Orticochea.³³ Grafting of defects or donor sites leaves a visible area of alopecia. Tissue expansion has been very successful in replacing scarred or grafted regions with hair-bearing skin. Defects larger than 8 to 10 cm are best treated with microsurgical free tissue transfer. Total or subtotal scalp avulsions are rare injuries that usually occur when a person's long hair becomes caught in rotating machinery. These potentially devastating injuries are ideally treated by scalp replantation, because the avulsed segment usually has preserved vessels (Fig. 45-38).

Calvarial Reconstruction. Autogenous bone remains the material of choice for reconstruction of skull defects. Its advantages include resistance to infection and ability to heal with strength. All autogenous bone sources have the disadvantage of donor site morbidity. Bone grafts can be harvested from a normal area of the calvaria, of which the outer table may be used as a graft for defects of limited size. Care must be taken during harvest to avoid compromise of the inner table. Rib bone may also be used, either as a split-rib graft or as a microsurgical free osseous flap. Unfortunately, use of ribs to reconstruct the skull may give an unappealing “washboard” appearance to the scalp. Another disadvantage of bone grafts, although not flaps, is graft resorption over time.

Alternative materials to autogenous bone exist for calvarial reconstruction, including methyl methacrylate, titanium, and hydroxyapatite (with or without bone morphogenic protein). Although they have the advantage of no donor site, these plastics and metals are associated with a higher risk of infection necessitating removal. Various formulations of calcium phosphate hydroxyapatites are being actively studied as bone replacement materials.

Head and Neck Reconstruction

The head and neck region has a compact arrangement of critical and complex structures encasing the essential routes to the gastrointestinal and respiratory systems. The tissues of the face, mouth, and cavities serve as a primary communication interface with the external environment through facial and verbal expression. Therefore, cancer resections with adequate safety margins can be severely and multiply debilitating. The management of head and neck cancer patients demands an integrated multidisciplinary team approach that includes the skills of ablative and reconstructive surgeons, medical and radiation oncologists, pathologists, nutritionists, and functional and psychological rehabilitation specialists.

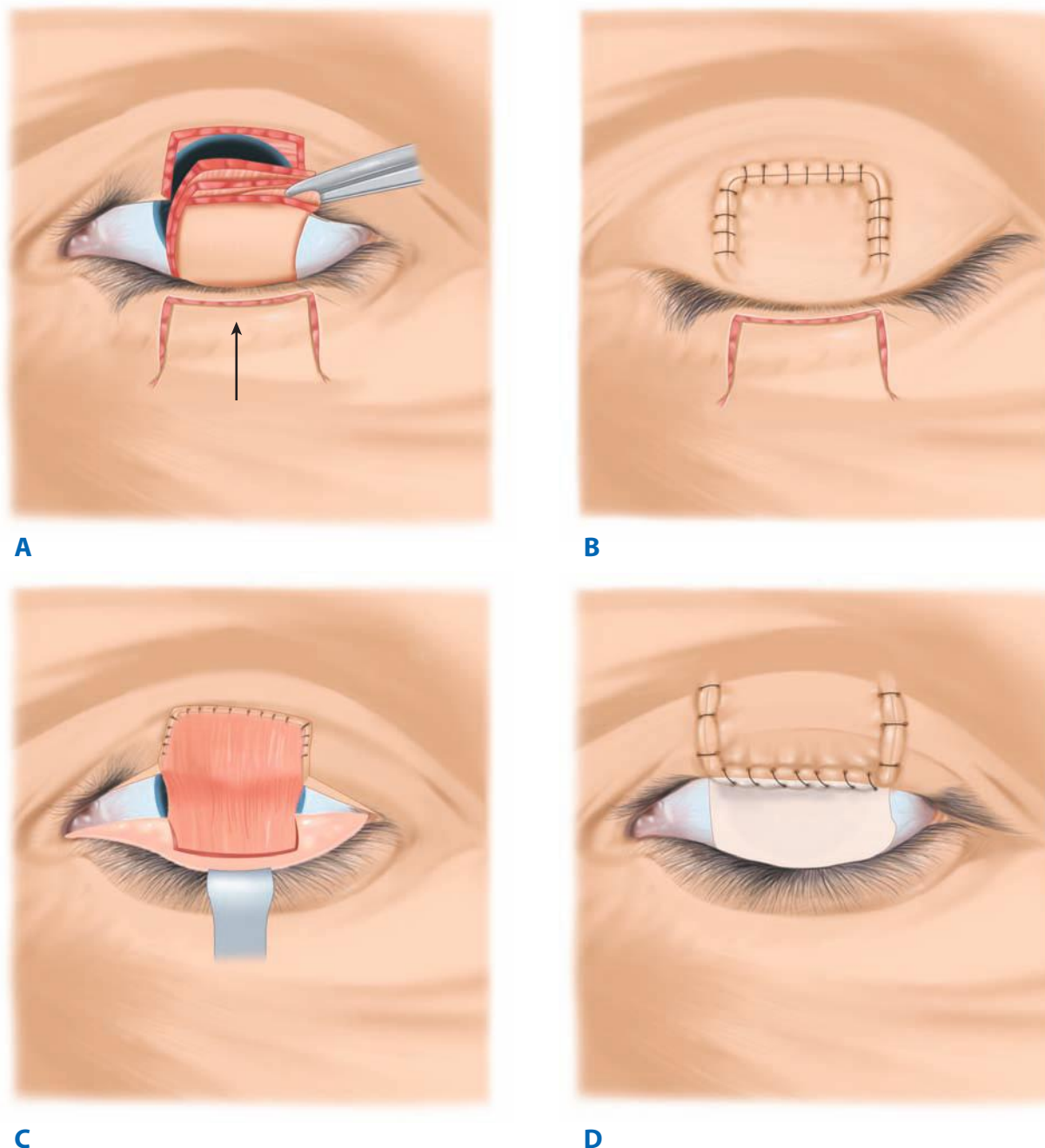


Figure 45-37. Upper eyelid defect of >50%. **A** and **B**, Cutler-Beard full-thickness lower eyelid advancement flap. **C** and **D**, Hughes lower eyelid tarsal conjunctival advancement flap. (Reproduced with permission from Pham RT. *Reconstruction of the upper eyelid*. Otolaryngol Clin North Am. 2005;38:1023. Copyright Elsevier.)

Table 45-11

Eyelid ptosis classification

Classification of ptosis severity	
Mild	1–2 mm
Moderate	3 mm
Severe	4+ mm
Classification of levator function	
Excellent	12–15 mm
Good	8–12 mm
Fair	5–7 mm
Poor	2–4 mm

Tumor-Ablative Surgery. The freedom available to the ablative surgeon to completely excise a tumor is limited, at least partly, by the capability of the reconstructive surgeon to restore anatomic continuity and achieve successful wound healing. A neck dissection to remove cervical lymphatics and nodes may be performed for prophylactic or curative intent, for more accurate prognostication by operative staging, and/or for solidification of plans for adjunctive treatments. It is important to be familiar with the tumor-node-metastasis (TNM) classification and staging of head and neck cancers. The N and M parameters are fairly constant for most head and neck cancers, whereas the T parameter varies according to tumor location.



Figure 45-38. Twenty-five-year-old woman with 70% scalp avulsion after a pedestrian-automobile accident. *Top row:* Defect and specimen intraoperatively. *Bottom row:* Appearance 9 weeks after microsurgical scalp replantation. (Photographs reproduced with permission from M. Gimbel.)

Principles of Reconstruction. The reconstructive surgeon aims to restore lost anatomic components adequately. Residual deficits, seemingly inconsequential, may progress to psychological morbidity, societal malacceptance, and social withdrawal. Uncomplicated and timely wound healing is important to allow adjuvant therapies when indicated and smooth discharge to home and occupation.

Each defect can be addressed by a number of methods, but the technique must be decided for each individual patient. Although a more complex reconstruction might offer improved outcomes, it may bring an increased risk of complications. Some patients may therefore benefit from use of a simpler method with more acceptable anesthetic and operative risk rather than a gold-standard reconstruction. Such an approach may be appropriate, for example, for an elderly patient with an advanced T4 cancer and short life expectancy. Reconstruction is impossible for some functional losses, such as the enucleation of an eye, but replacement by a reasonably aesthetic prosthesis may be achievable.³⁴

Reconstructive Options by Region. Before the 1970s, autogenous tissue reconstructions were largely restricted to local or regional pedicled flaps, including the trapezius, pectoralis, and deltopectoral workhorse flaps. With microvascular free tissue transplantation, defects that were previously deemed nearly impossible to reconstruct can now be addressed in a single operation. Consequently, head and neck cancers that were historically unresectable have become more operable.

Intraoral Structures The reconstructive choice for floor of mouth, tongue, and other intraoral defects is dictated by the dimension of the defect, the volume of tissue lost, and residual tongue mobility. The tongue and adjacent mucosal surfaces heal exceptionally well, so small defects may be treated by primary closure or even left to heal spontaneously. Smaller defects, less than one-fourth glossectomy, may be treated with a skin graft or perhaps primary closure if tongue mobility is preserved. Larger defects, more than one-third glossectomy, call for reconstruction by free tissue transfer, commonly a free radial forearm or anterolateral thigh flap for smaller- or larger-volume defects,

respectively. Total glossectomy defects are a major challenge, and no ideal method exists to restore tongue motor functions. The primary goal is to protect the airway from aspiration. Swallowing and articulation are often suboptimal after total glossectomy reconstructions. Options include bulkier myocutaneous free flaps harvested from the anterolateral thigh, the back (latissimus dorsi), or the abdomen (rectus abdominis), or pedicled regional flaps (e.g., latissimus dorsi).³⁵

The reconstructive choice for other intraoral soft tissue defects should also take into consideration the specific characteristics of the defect, such as its thickness and dimensions, and involvement of the oral commissure, facial skin, and/or neck. Buccal defects, for example, may be adequately treated with a radial forearm free flap or a thin anterolateral thigh flap. Thicker defects may be more appropriately reconstructed with a fasciocutaneous anterolateral thigh free flap. Those that extend through the full thickness of the cheek to involve the external facial skin may be reconstructed with a cutaneous or myocutaneous anterolateral thigh free flap that has been folded to address the internal mucosal, external skin, and intervening soft tissue defects simultaneously.³⁶ When the contour of the neck is expected to be sunken and asymmetric after a neck dissection, it is possible to improve symmetry by inseting part of the flap into the neck. This maneuver also obliterates dead space and helps protect the adjacent major neurovascular structures.

Mandible and Midface Mandibular defects may arise from the ablation of tumors involving the bone itself or from the need to satisfy clearance margins for adjacent soft tissue tumors. Segmental mandibular defects can be classified as isolated bone defects, compound defects (bone and oral lining *or* skin), composite defects (bone, oral lining, *and* skin), or extensive composite defects (bone, oral lining, skin, and soft tissues).³⁷ The primary goals of mandibular reconstruction are to restore bony continuity, masticatory (with accurate dental occlusion) and speech functions, and facial contour, and to maintain tongue mobility. Occasionally, a small segmental mandibular defect may be amenable to reconstruction with a nonvascularized bone graft, but these are poorly suited to the forces of mastication and are prone to resorption and failure amid radiotherapy or infection.

The best option for most segmental mandibular defects is the fibula bone free flap with an adjoined skin island supplied by reliable septocutaneous vessels (occasionally musculocutaneous perforators) from the peroneal artery and vein; this is termed a *fibula osteoseptocutaneous free flap*.³⁸ Its many desirable characteristics include (a) the ability to withstand multiple osteotomies (as long as the periosteal blood supply is protected) so that the bone can be folded to re-create the contour of any mandibular region, (b) an unmatched supply of sturdy bone length (22–26 cm in the adult) sufficient to reconstruct even angle-to-angle defects, (c) a bicorticocancellous structure that can tolerate the forces of mastication as well as the incorporation of osseointegrated dental implants, (d) acceptable donor site morbidity when the flap is appropriately harvested, and (e) a donor site location that allows a two-team approach for simultaneous tumor ablation and flap harvest.^{39,40} Reasonable alternatives include vascularized bone flaps from the iliac crest, radius, or ribs. Extensive composite mandibular defects may demand more than one free flap (such as one anterolateral thigh free flap with one fibula osteoseptocutaneous free flap) to reconstruct the

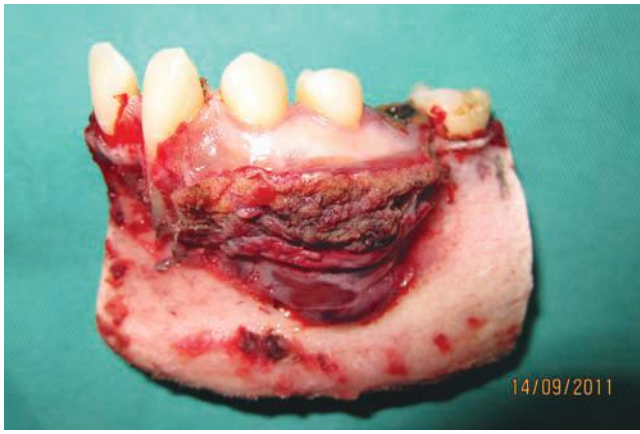
entire anatomy in one operation.⁴¹ Later, dental rehabilitation can be achieved with conventional dentures if alveolar ridge height and soft tissue quality allow. However, for select patients, osseointegrated dental implants offer a far superior alternative. These can be secured into the neomandible, either at the time of reconstruction (primarily; Fig. 45-39) or more commonly at a later stage (secondarily), and ultimately will support a dental prosthesis that can closely match the native dentition for excellent aesthetic and masticatory outcomes.⁴²

Similar principles are also applicable to other bony defects in the head and neck region, including maxillary and other midfacial defects, although non-load-bearing, facial, bone-only defects may be more amenable to nonvascularized bone grafting such as from the calvarium. The goals of midface reconstruction include the restoration of facial contour and projection, achievement of accurately occlusive maxillary dentition, provision of appropriate infraocular support, and sealed separation of adjacent nasal and oral cavities.

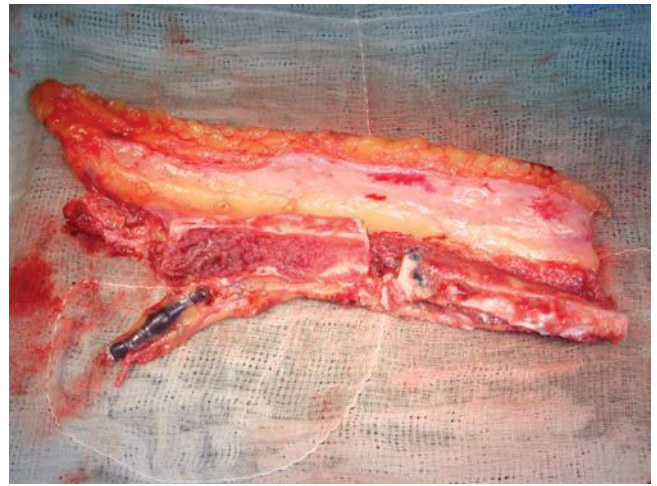
Esophagus and Hypopharynx The goals of reconstruction for esophageal and hypopharyngeal defects, which may be circumferential or partial, are to maintain luminal patency, restore speech and swallowing, and avoid strictures, fistulas, and gastrointestinal anastomotic leaks. Reconstructive options for partial defects include primary closure, if luminal narrowing is insignificant, and skin (or dermal) grafts for partial-lining defects. A regional muscle flap may be useful for patching small full-thickness defects, but larger defects call for free tissue transfer of a jejunal flap or a tubed fasciocutaneous flap.⁴³ The jejunal flap involves the harvest of a proximal segment based on its mesenteric blood supply and inset into the neck in the isoperistaltic direction. Disadvantages of the jejunal flap include halitosis, slow swallowing transit times, and a “wet” voice. Tubed fasciocutaneous free flap options, including the anterolateral thigh and radial forearm flaps, are also popular; however, they may have a greater risk of stricturing than the free jejunal flap. Nevertheless, proponents of such flaps favor the resultant vocal qualities and faster transit times.

Recipient Vessels in the Head and Neck for Free Flaps Commonly used recipient arteries for free tissue transfer in the head and neck include the ipsilateral superior thyroid, lingual, facial, superficial temporal, and transverse cervical arteries. End-to-side anastomosis with the carotid artery is associated with potentially lethal carotid blow-out injury. Anastomoses with contralateral vessels are useful when ipsilateral vessels are not available, such as in patients with recurrent cancer who have undergone previous free flap procedures or irradiation.³⁶ Vein grafts can be avoided by using carefully planned flaps that offer longer pedicles (such as the anterolateral thigh of fibula osteoseptocutaneous free flaps) but may occasionally be necessary. For venous drainage, tributaries of the superficial and deep jugular systems are convenient. Finally, protection of the major vessels and nerves of the neck is possible after neck dissection by overlaying residual free flap tissues. This also aids in improving the contour and symmetry of the neck for aesthetic purposes and obliterates any dead space.

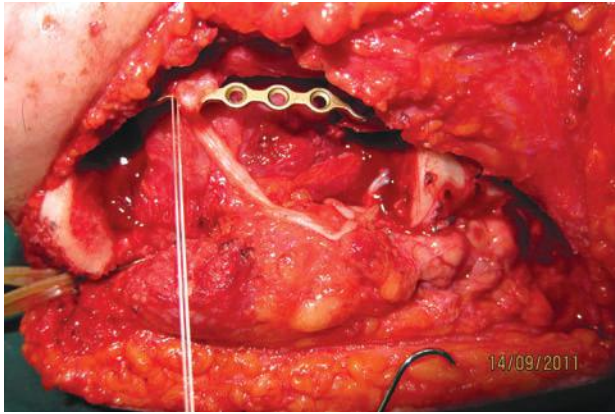
Complications Apart from the general complications that may be encountered with any major operation, there are several specific potential complications of head and neck ablative and reconstructive surgery. Specific intraoperative complications include air embolus, pneumothorax, and injuries to important



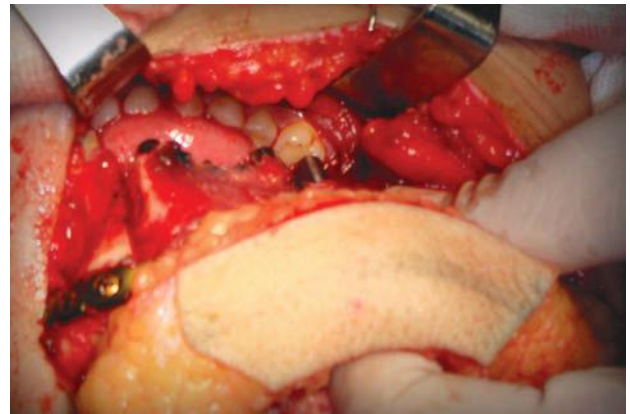
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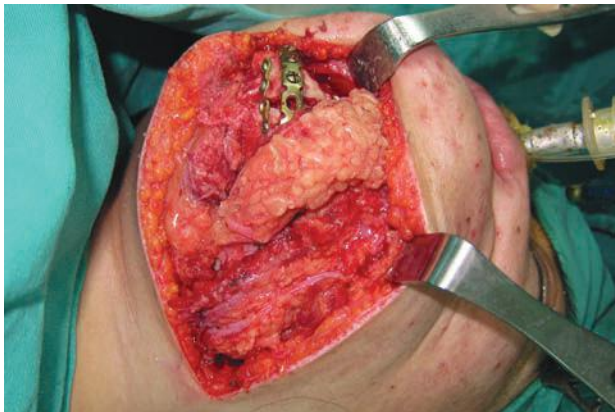
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F

Figure 45-39. Free double-barreled fibula osteoseptocutaneous flap with primary osseointegrated dental implants used to reconstruct a compound segmental mandibular defect from ameloblastoma resection. **A.** Left parasymphysal segmental mandibulectomy with contiguous dentition and oral lining. **B.** The osteotomized fibula osteoseptocutaneous free flap ready to be double-barreled; note that a segment of bone between the two struts (barrels) has been discarded to allow safe folding of the construct without compression or kinking of the intervening periosteal blood supply. **C.** Segmental reconstruction of the resected inferior alveolar nerve with a cutaneous nerve graft from the fibula donor site to restore mentolabial sensation; note the extent of the segmental mandibular defect. **D.** Three osseointegrated dental fixtures have been loaded into the upper barrel of the fibula; abutments are fitted to the fixtures to allow accurate occlusal matching with the corresponding maxillary dentition before finalizing fibula fixation. **E.** The de-epithelialized portion of the skin paddle was used to cover the reconstruction plate as well as to contour the soft tissue profile of the neomandibular margin. **F.** The skin paddle has been inset to reconstruct the oral lining; note that the fibula osteoseptocutaneous flap is best raised with a skin paddle even when there is no cutaneous defect so that it can provide a sentinel flap monitor of the underlying bone as well as facilitate wound closure. At this point, the dental fixtures are sealed with cover plates under the flap skin paddle but will later be fitted with final abutments and a dental prosthesis. **G.** Panorex radiograph: By 5 months postoperatively, the fibula had consolidated with the native mandible. **H** and **I.** At 10 months, the patient has an aesthetic neomandibular margin as well as functional and accurate occlusion after finalization with a dental prosthesis. (Photographs reproduced with permission from F. Wei.)



G



H



I

Figure 45-39. (Continued)

vessels, lymphatics, or cranial nerves. Specific perioperative complications include carotid artery blow-out, flap necrosis, infections, saliva or chyle leakage, airway problems, and acute psychiatric disturbances. Examples of later complications are prolonged pain syndromes, fistulas, scar contractures, and problems associated with radiotherapy such as flap shrinkage (potentially with metalwork exposure) and osteoradionecrosis.

Facial Reanimation

Facial nerve paralysis is a debilitating and emotionally depressing condition that presents many functional and aesthetic problems. Loss of mimetic muscle activity leads to poor articulation and drooling from oral incompetence, exposure keratopathy from dysfunctional lacrimation and paralytic ectropion, and impaired socialization from facial disfigurement and difficulty expressing emotion. Facial nerve dysfunction has a number of possible causes, including oncologic resection, temporal bone or skull base surgery, trauma, congenital conditions (Möbius' syndrome), and idiopathic origin. The main considerations in treatment are management of forehead and brow symmetry, eyelid closure, oral competence and symmetry, and smile dynamics. The long-term goals include normal static appearance, symmetry with movement, and restoration of voluntary muscular control. Although the best results usually require multistaged, complex surgeries, the elderly patient is better

served by a single-stage procedure that provides immediate improvement.

Neural Techniques. Traumatic injuries to the facial nerve without segmental nerve loss are best treated with primary end-to-end neuroorrhaphy of the facial nerve stumps. The success of this repair depends on accurate approximation of nerve ends and achievement of a tension-free epineural repair with fine sutures. In segmental facial nerve loss due to trauma or oncologic resection, interpositional nerve grafts lead to the most successful reconstruction and may approach the results of primary repair. Grafting ideally is performed at the time of the injury rather than in delayed fashion. Donor nerves include the cervical plexus, great auricular nerve, and sural nerve. Timing of reanimation after nerve repair depends on distance of the repair from the motor end plates. Axonal regeneration proceeds at approximately 1 mm/d, whereas motor end plates deteriorate at approximately 1% per week and are gone by 2 to 3 years. In general, facial tone returns approximately 6 months after repair and voluntary motion a few months later.⁴⁴ Problems associated with facial nerve repair and grafting are weakness, mass movement (synkinesia), and dyskinesia. If the proximal facial nerve stump is available but the distal stumps are not, the cervical plexus can be harvested and proximally anastomosed to the facial nerve stump and distally implanted into the mimetic muscles to allow neurotization and partial restoration of function.

Nerve transfer techniques borrow other local cranial nerves to innervate the distal facial nerve stump if grafting cannot be done. This requires the availability of distal facial nerve or nerve branch stumps. Typically used donor nerves include the ipsilateral hypoglossal nerve, spinal accessory nerve, and cross-face sural nerve graft from a contralateral facial nerve branch (redundant buccal or zygomatic branch). Disadvantages of this technique include those of nerve repair or grafting plus loss of donor nerve function and facial hypertonia. Transfer of the complete hypoglossal nerve creates ipsilateral tongue paralysis and hemitongue atrophy with mild to moderate intraoral dysfunction.⁴⁴

Muscle Transposition Techniques. All of the aforementioned neural techniques rely on the presence of a functional distal neuromuscular unit. When the distal neuromuscular unit is deficient, as in congenital facial paralysis or in situations in which reconstruction is not undertaken until 2 to 3 years after the original insult, muscle transposition is considered. Muscle transposition techniques require intense muscular retraining to achieve the intended dynamics. A classic muscle dynamic facial sling uses the temporalis muscle, innervated by the trigeminal nerve and perfused by the deep temporal branch of the internal maxillary artery. The muscle is released along with its aponeurosis from the temporal fusion line, reflected inferomedially, and attached to the modiolus at the oral commissure, the nasolabial fold, and potentially the orbicularis oculi. Disadvantages include lack of spontaneous movement, temporomandibular joint dysfunction, and soft tissue fullness over the zygomatic arch. Other transferable muscle units include the masseter muscle and the anterior belly of the digastric muscle.⁴⁴

Innervated Free Tissue Transfer. Microsurgical free innervated muscle transfer may be considered in the same situations as local muscle transfers but is especially appropriate when concomitant soft tissue augmentation is needed. Muscles described for this purpose include the gracilis, latissimus dorsi, serratus anterior, and pectoralis minor muscles. The procedure may be performed in a single stage if the proximal facial nerve stump is available for anastomosis or if a long enough donor muscle nerve is present to reach the contralateral facial nerve branches. Often, however, it is a staged procedure beginning with establishment of a local neural source via cross-facial nerve grafting. The extent of axonal regeneration through the graft is monitored using Tinel's test. After sufficient axonal progression, approximately 6 to 12 months, the free muscle transfer is performed via vascular anastomoses to the superficial temporal or facial vessels, recipient and donor nerve coaptation, and fixation of the muscle to the zygoma superolaterally and to the nasolabial fold, upper lip orbicularis, and lower lip orbicularis inferomedially. Disadvantages of free muscle transfer include donor site morbidity, lengthy surgical times, and the need for specialized microsurgical skills.

Ancillary Procedures. One of the most important goals of treatment for facial paralysis is rehabilitation of the periocular region. This objective may be simply achieved with implantation of gold or platinum upper eyelid weights, which allows gravity to assist with lid closure. Static fascial slings are used to improve symmetry when comorbid conditions preclude more extensive and staged surgeries. Sling materials include tensor fasciae latae, Gore-Tex, and human acellular dermal allograft. Nonsurgical techniques play a significant role in improving facial symmetry, both as a primary intervention and an adjunct to surgery. Contralateral mimetic muscle hypertonicity is

tempered with botulinum toxin injections. Finally, soft tissue rejuvenative techniques such as cervicofacial rhytidectomy, blepharoplasty, browlift, and midface lift can improve the soft tissue effects of facial nerve paralysis (Fig. 45-40).

Breast Reconstruction

Breast cancer is the most common malignancy and the second leading cause of cancer-related death among women in the United States. One in eight women will develop breast cancer sometime during their life. Breast reconstruction began as a means to reduce chest wall complications and deformities from mastectomy. Reconstruction has now been shown to benefit women in terms of psychological well-being and quality of life.⁴⁵ The goal of breast reconstruction is to re-create form and symmetry while avoiding delay in adjuvant cancer treatment. A number of studies have shown that breast reconstruction, both immediate and delayed, does not impede standard oncologic treatment, does not delay detection of recurrent cancer, and does not change the overall mortality associated with the disease.⁴⁶⁻⁴⁸

Preoperative counseling of the breast cancer patient regarding reconstruction options should include discussion of the timing and type of reconstruction, alternatives to surgical reconstruction, and realistic expectations. The plastic surgeon and surgical oncologist must maintain close communication to achieve optimal results.

Timing of Reconstruction. *Immediate reconstruction* is defined as initiation of the breast reconstructive process at the time of the ablative surgery. This is usually done in patients with early-stage disease for whom there is low expectation of postoperative radiation therapy. Immediate reconstruction takes advantage of the preserved, supple skin envelope made possible by the skin-sparing mastectomy approach. In general, this allows a more aesthetically pleasing and symmetric reconstruction. It is also psychologically advantageous to the patient to avoid living with the mastectomy deformity, as in delayed reconstruction. Furthermore, the cost to the medical system is less with immediate reconstruction because fewer operations are required than for staged procedures. Disadvantages include the potential delay of adjuvant therapy due to surgical site complication, partial necrosis of mastectomy skin flaps, and the possibility that unanticipated postoperative radiation therapy is required. Breast reconstructions by all techniques are adversely affected by radiation therapy, and many surgeons feel reconstruction should be delayed until at least 6 months after treatment.

Delayed breast reconstruction is initiated at least 3 to 6 months after mastectomy. This approach avoids mastectomy flap unreliability and radiation therapy unpredictability. However, the patient is subjected to an additional operative procedure, and overall cosmetic result is often worse (especially with autologous tissue reconstruction).

Partial Breast Reconstruction. Over the last decade, many women have chosen breast conservation therapy (BCT) consisting of segmental mastectomy with sentinel lymph node biopsy and/or axillary lymph node dissection combined with postoperative whole-breast irradiation. Although this less invasive cancer treatment is quite beneficial to many women, significant breast deformity can result from the tissue removal and radiation-induced changes, especially in women with small breasts. *Oncoplastic surgery* refers to the set of techniques developed to lessen breast deformity from partial mastectomy, both

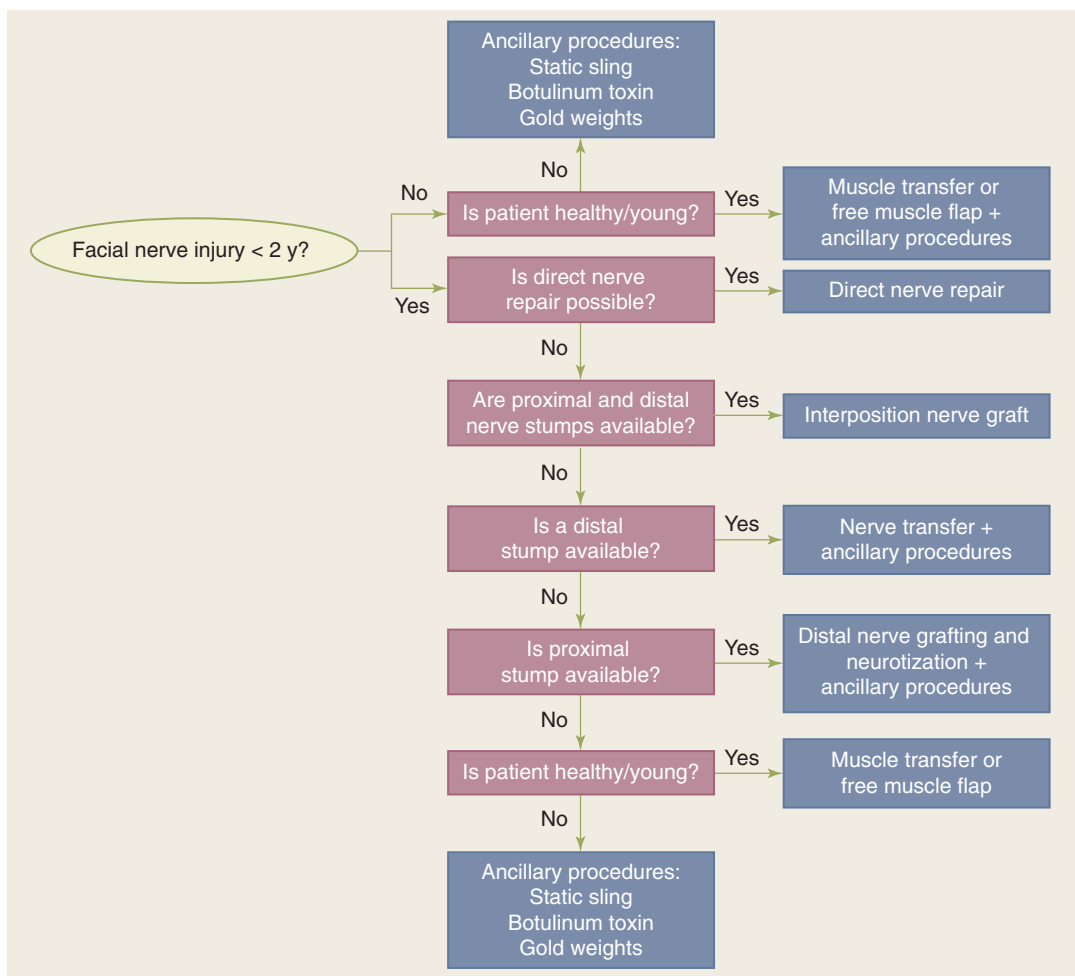


Figure 45-40. Facial reanimation treatment algorithm.

in the delayed and the immediate settings. One of the most common methods of minimizing defect visibility in large-breasted women is to rearrange the breast parenchyma at the time of tumor extirpation using reduction mammoplasty techniques. Dermatoglandular pedicles supporting the nipple-areolar complex can be designed in any number of orientations to avoid the defect location. This procedure, combined with traditional contralateral breast reduction, can result in excellent cosmetic outcomes, often better than the preoperative appearance (Fig. 45-41). The lateral thoracodorsal flap, based on the lateral intercostal perforators at the inframammary fold, is particularly useful in correcting lateral breast defects⁴⁹

One drawback of these oncoplastic techniques when performed at the time of segmental mastectomy is the chance that, if the specimen margins are not clear, the reconstruction must be taken down to allow for reexcision. The oncologic implications of reusing the flap in this setting are unclear. Another shortcoming is the potential for fat necrosis, especially distally, in these nonaxial pattern flaps.

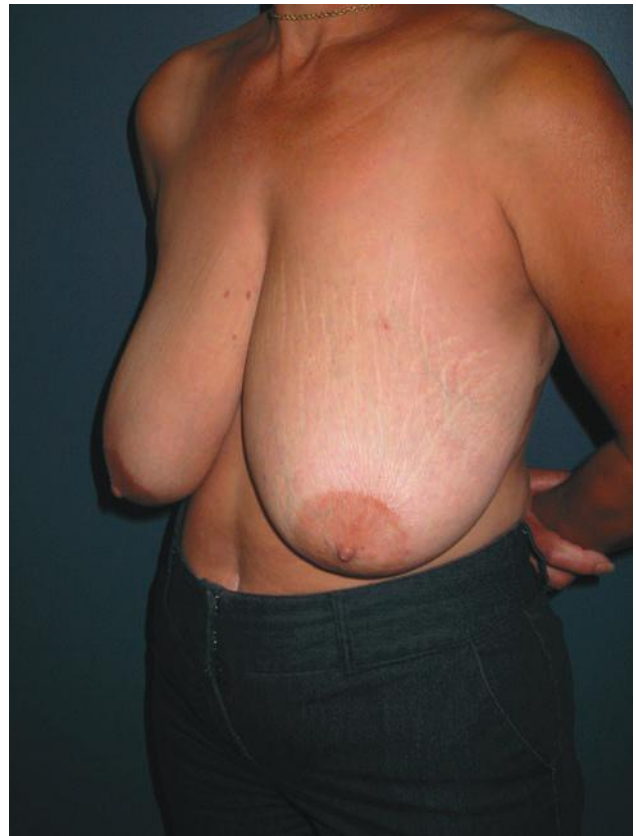
Implant-Based Reconstruction. By necessity or patient choice, many women undergo mastectomy for local control of breast cancer. In fact, recently in response to the increased recognition of multifocal disease and experience with poor aesthetic results after BCT in small-breasted patients, some women have chosen mastectomy despite being candidates for BCT.

The simplest method of reconstructing the breast is placement of an implant into the mastectomy defect. Occasionally an implant may be placed at the time of mastectomy as a one-stage mound reconstruction. Usually, however, the first stage involves placement of a silicone shell tissue expander under the chest wall musculature (pectoralis major, serratus anterior, superior rectus sheath), followed by expansion of the skin and pocket regularly over the following few months. The patient then returns to the operating room for removal of the expander and placement of a saline or silicone breast implant (Figs. 45-42 and 45-43). After exhaustive investigation, silicone implants have been proven as safe and effective as saline implants in breast augmentation and reconstruction. After another few months, the nipple is reconstructed.

The advantages of the tissue expander/implant-based reconstruction are absence of donor site morbidity, short operative times, and short recovery periods. The disadvantages include the need for more reconstructive stages and longer cumulative time to completion of reconstruction. Implant breast reconstructions tend to lack the natural breast feel and ptotic appearance. This is particularly noticeable in unilateral reconstructions. Some of these disadvantages have been mitigated by the advent of nipple-sparing mastectomy and immediate, acellular dermal matrix-assisted implant reconstruction (Fig. 45-44). Complications related to prosthetic-based breast reconstruction include infection, malposition, hematoma, seroma, and rupture



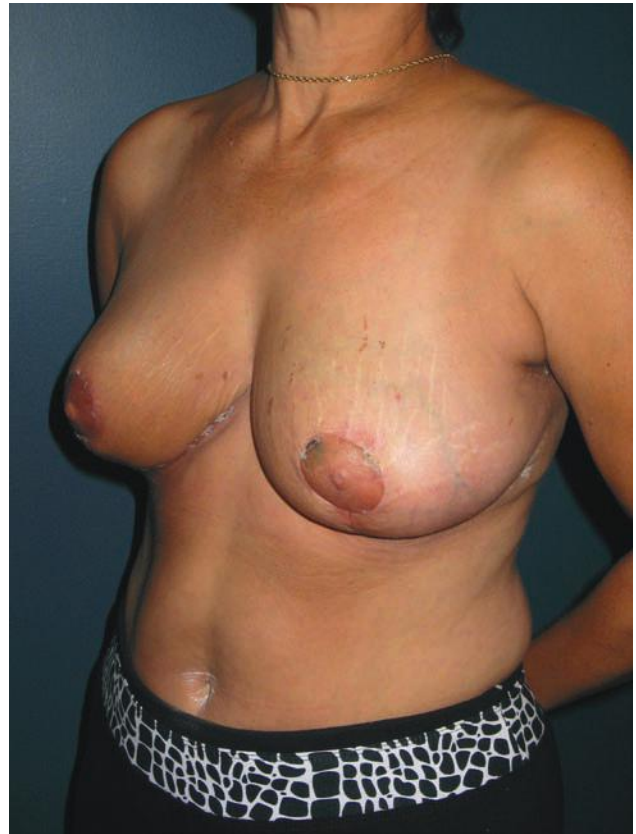
A



B



C



D

Figure 45-41. Preoperative (*top row*) and 3-week postoperative (*bottom row*) photos of a 52-year-old patient with cancer at the 6 o'clock position of the left breast. Oncoplastic superomedial pedicle reduction on the left breast was performed simultaneously with a left segmental mastectomy of the lesion and a contralateral symmetrization reduction. (*Photographs reproduced with permission from M. Gimbel.*)

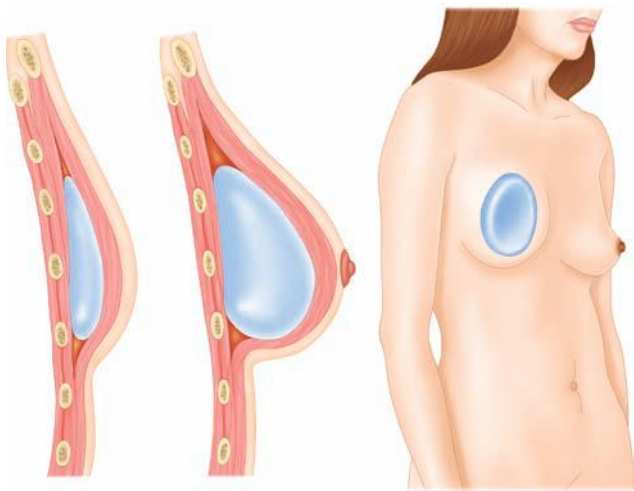


Figure 45-42. Tissue expansion and implant-based breast reconstruction. (Illustrations reproduced with permission from M. Gimbel.)

and deflation. Long term, the most common problem requiring reoperation is the formation of dense scarring around the implant (capsular contracture) causing firmness, visible deformity, and even discomfort. In addition, implants are medical devices that undergo mechanical wear, ultimately leading to leakage and deflation. All in all, the chance that a woman will need additional unanticipated surgery on her reconstructed breast within 5 years of prosthetic-based reconstruction is approximately 35%.⁵⁰

The cosmetic results worsen and the rate of complications increases when implants are placed in an irradiated chest wall, regardless of whether the radiation therapy occurs before or after reconstruction.

Total Autologous Tissue Reconstruction. An entirely different way to reconstruct the breast avoids the placement of implants in favor of using only the patient's own redundant tissue. Indications for total autologous breast reconstruction are many and varied, including patient preference, previous or anticipated chest wall radiation treatment, a ptotic contralateral breast, and previous failed implant reconstruction. Contraindications are lack of a suitable donor site due to scarring or minimal adiposity, morbid obesity, and serious comorbidities that preclude a longer surgery and recovery period.

The most commonly used donor site is the abdomen. Most women in the breast cancer patient population have redundant skin and fat in the lower abdomen that may be transferred to the chest wall and fashioned into a breast mound. Many techniques have been developed to transfer this tissue, both as pedicled myocutaneous flaps and as free flaps. The workhorse abdominal flap for breast reconstruction is the pedicled transverse rectus abdominis myocutaneous (TRAM) flap. This flap is based on the superior epigastric vessels that run on the undersurface of the rectus abdominis muscle. A transversely oriented skin paddle with underlying fat is isolated based on its perforating vessels that course through the rectus muscle to join the main superior epigastric pedicle. The flap, along with the rectus muscle and blood supply, is tunneled under the anterior chest wall and



A



B

Figure 45-43. Bilateral tissue expander/implant-based breast reconstruction. Appearance preoperatively (**A**) and 2 months after saline implant exchange (**B**). (Photographs reproduced with permission from M. Gimbel.)

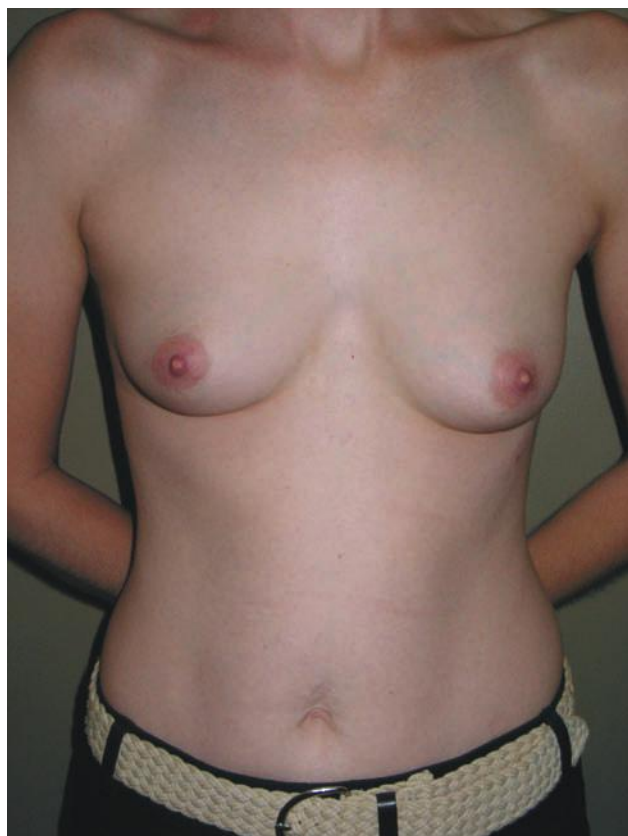
**A****B****C****D**

Figure 45-44. Immediate single-stage implant-based breast reconstruction after bilateral prophylactic nipple-sparing mastectomy (NSM). **A.** Preoperative photo. **B.** Postoperative photo after bilateral NSM and immediate acellular dermal matrix-assisted silicone gel implant reconstruction. (Photographs reproduced with permission from M. Gimbel.)

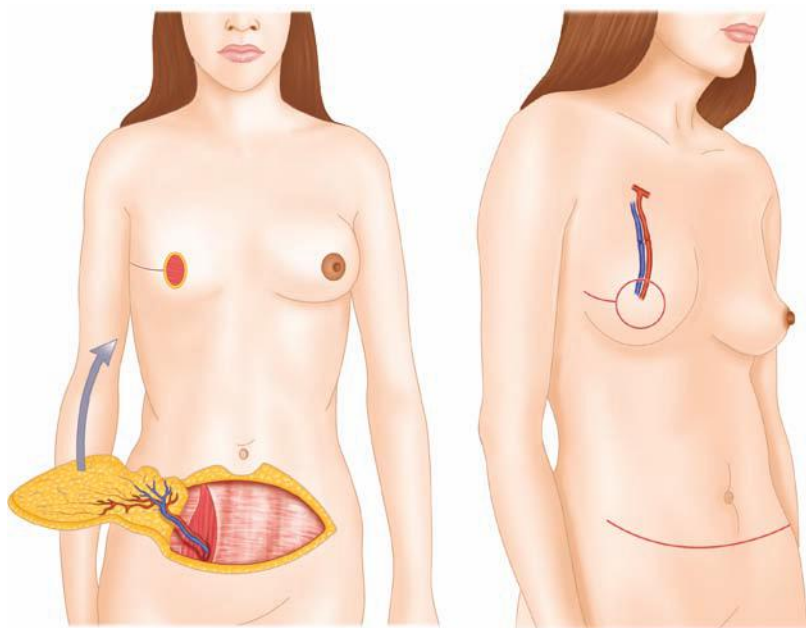


Figure 45-45. Deep inferior epigastric perforator flap breast reconstruction. (Illustrations reproduced with permission from M. Gimbel.)

delivered into the mastectomy defect, where it is then shaped into a breast mound. The donor site is closed in a manner similar to an abdominoplasty. The advantages of this and all total autologous reconstruction techniques are creation of a breast that looks and feels natural, that changes volume along with the patient's weight (and the contralateral natural breast), and that avoids the potential complications of breast implants. In addition, patients are often pleased to have the incidental benefit of an abdominoplasty. The pedicled TRAM flap procedure is also relatively quick for a total autologous reconstruction. Downsides include the potential for partial or complete flap failure, fat necrosis, fullness in the upper abdomen from the tunneled pedicle, abdominal wall bulge or hernia, and abdominal wall weakness.

The free TRAM flap was introduced to improve on the sometimes limited volume of tissue that can be carried by the relatively indirect blood supply of the pedicled TRAM's superior epigastric vessels. The free TRAM flap is similar to the pedicled TRAM flap but is based on the deep inferior epigastric vessels, which are the dominant blood supply to the lower abdomen. The flap is harvested as a free flap, and the deep inferior epigastric artery and vein are anastomosed to recipient vessels in the chest, usually the internal mammary or the thoracodorsal vessels. A refinement to this method is the muscle-sparing free TRAM flap procedure, in which less fascia and rectus abdominis muscle is harvested with the flap to minimize donor site morbidity. The ultimate muscle-sparing free TRAM flap is the deep inferior epigastric perforator flap (Fig. 45-45). In this case, the fascia is opened but no muscle is included with the flap, and the perforating vessels of the deep inferior epigastric system are dissected between the muscle fibers to join the main pedicle. When patients are carefully selected, muscle-sparing techniques decrease abdominal wall morbidity and increase useful pedicle length for microsurgery without significantly compromising flap perfusion⁵¹ (Fig. 45-46A,B). Finally, in some patients, the lower abdominal tissue may be transferred to the breast as a free flap without violating the abdominal wall fascia at all. The superficial inferior epigastric artery is often capable of supporting enough abdominal

tissue volume to reconstruct the breast. Because this artery and its accompanying vein do not traverse the anterior rectus sheath, the flap can be harvested with no more abdominal wall morbidity than an abdominoplasty. Unfortunately, this artery is frequently absent or too diminutive in size to be used in the majority of patients. Despite the many advantages of microsurgical total autologous breast reconstruction, it is associated with longer operative times than pedicled TRAM procedures, requires expertise in microsurgery, and has the potential for complete flap failure due to microvascular thrombosis.

Implant and Autologous Tissue Reconstruction. The pedicled latissimus dorsi myocutaneous flap procedure is a straightforward, reliable method used for breast reconstruction. It is often reserved for reconstructing breasts when other methods have previously failed. The latissimus flap is relegated to second-choice status because it carries the major disadvantage of autologous tissue reconstruction (donor site morbidity) as well as all of the potential complications associated with breast implants. That aside, the latissimus flap/implant-based reconstruction can produce excellent cosmetic results with relatively low donor site morbidity (Fig. 45-47). The latissimus dorsi muscle with overlying skin paddle is elevated based on its thoracodorsal vessel pedicle, tunneled through the axilla, and delivered into the mastectomy site. After partial inset, either a tissue expander or permanent implant is usually placed behind the muscle to give adequate volume to the reconstruction (Fig. 45-48). Drawbacks specific to this method include contour irregularity of the back, high rate of donor site seroma, and shoulder weakness (uncommon).

Accessory Procedures. After creation of the breast mound, refinements and accessory procedures are performed after approximately 3 months. These may include breast mound revision, scar revisions, fat grafting, and nipple-areola complex reconstruction. Scores of methods have been described for reconstructing the nipple. These include local flap techniques (e.g., star flap, skate flap, C-V flap), grafting techniques (contralateral nipple/areola sharing, groin skin, labia skin), and tattooing.

Radiation-Related Considerations. With some notable exceptions, most surgeons advocate avoidance of implant-based breast reconstruction in chest walls that have previously received radiation or are likely to receive radiation due to the relatively high rate of complications and disappointing results. Delayed total autologous reconstructions bring healthy nonirradiated tissue to replace the damaged fibrotic tissue and are the preferred mode of breast reconstruction in this setting. Similarly, latissimus dorsi/implant reconstructions replace much of the irradiated skin, which probably explains to some degree why, in the face of previous irradiation, implants fair better with an overlying latissimus flap than without.

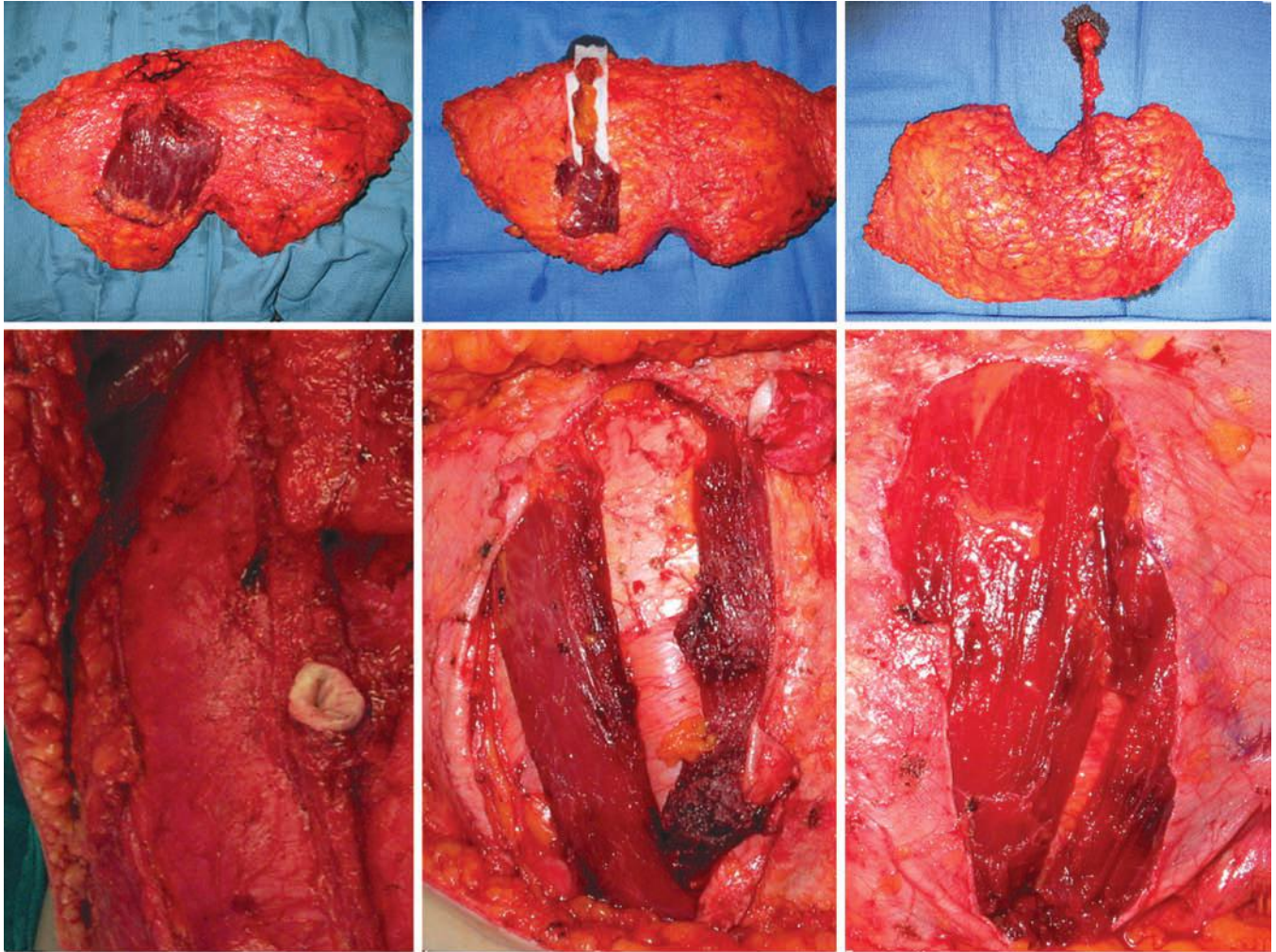
The question of whether total autologous reconstructions should be done before or after anticipated radiation therapy is still controversial. Those in favor of delaying the reconstruction argue that an irradiated flap will exhibit shrinkage and fibrosis that subtracts from the overall aesthetic result. Those in favor of performing immediate reconstruction in this setting feel that, because immediate reconstructions have inherently better aesthetics, the imperfect result due to irradiation it is still comparable to the result of delayed reconstruction without the additional

operation. To date, no prospective study has been performed comparing the two approaches.

Trunk and Abdominal Reconstruction

In the trunk, as in most areas of the body, choice of reconstructive method is determined by the location and size of the defect and the properties of the deficient tissue. A distinction is made between partial-thickness and full-thickness defects in deciding between grafts, flaps, synthetic materials, or a combination of techniques. Unlike the head and the lower leg, the trunk harbors a relative wealth of regional transposable axial pattern flaps that allow sturdy reconstruction, only rarely requiring distant free tissue transfer. Indeed, the trunk serves as the body's arsenal, providing its most robust flaps to rebuild its largest defects.

Thoracic Wall. The chest wall is a rigid framework designed to resist both the negative pressure associated with respiration and the positive pressure from coughing and from transmitted intra-abdominal forces. Furthermore, it protects the heart, lungs, and great vessels from external trauma. Reconstructions of chest wall defects must emulate these functions.



A
Figure 45-46. **A.** Left upper and lower panels: Free transverse rectus abdominis myocutaneous (FTRAM) flap and its donor site defect. Middle upper and lower panels: Muscle-sparing FTRAM flap and its donor site defect. Right upper and lower panels: Deep inferior epigastric perforator flap and its donor site defect. **B.** Preoperative and postoperative photos of a 43-year-old woman with a left muscle-sparing FTRAM breast reconstruction and right symmetrization reduction mammoplasty. (Photographs reproduced with permission from M. Gimbel.)

**B**

Figure 45-46. (Continued)

The pectoralis major muscle is the workhorse pedicled flap for coverage of the sternum, upper chest, and neck. It is a Mathes and Nahai type V flap with one dominant pedicle (pectoral branch of the thoracoacromial artery) and several secondary segmental pedicles (intercostal perforators and the pectoral branch of the lateral thoracic artery).⁵² The muscle may be advanced or transposed on its dominant pedicle or used as a

turnover flap based on its internal mammary perforators. Both methods are useful in covering the sternum after dehiscence or infection. Before the turnover flap is elevated, previous operative notes should be reviewed carefully to determine whether the internal mammary artery is still a viable perfusion source; the artery, especially the left, is frequently used for heart revascularization. The muscle may also be used for obliteration of

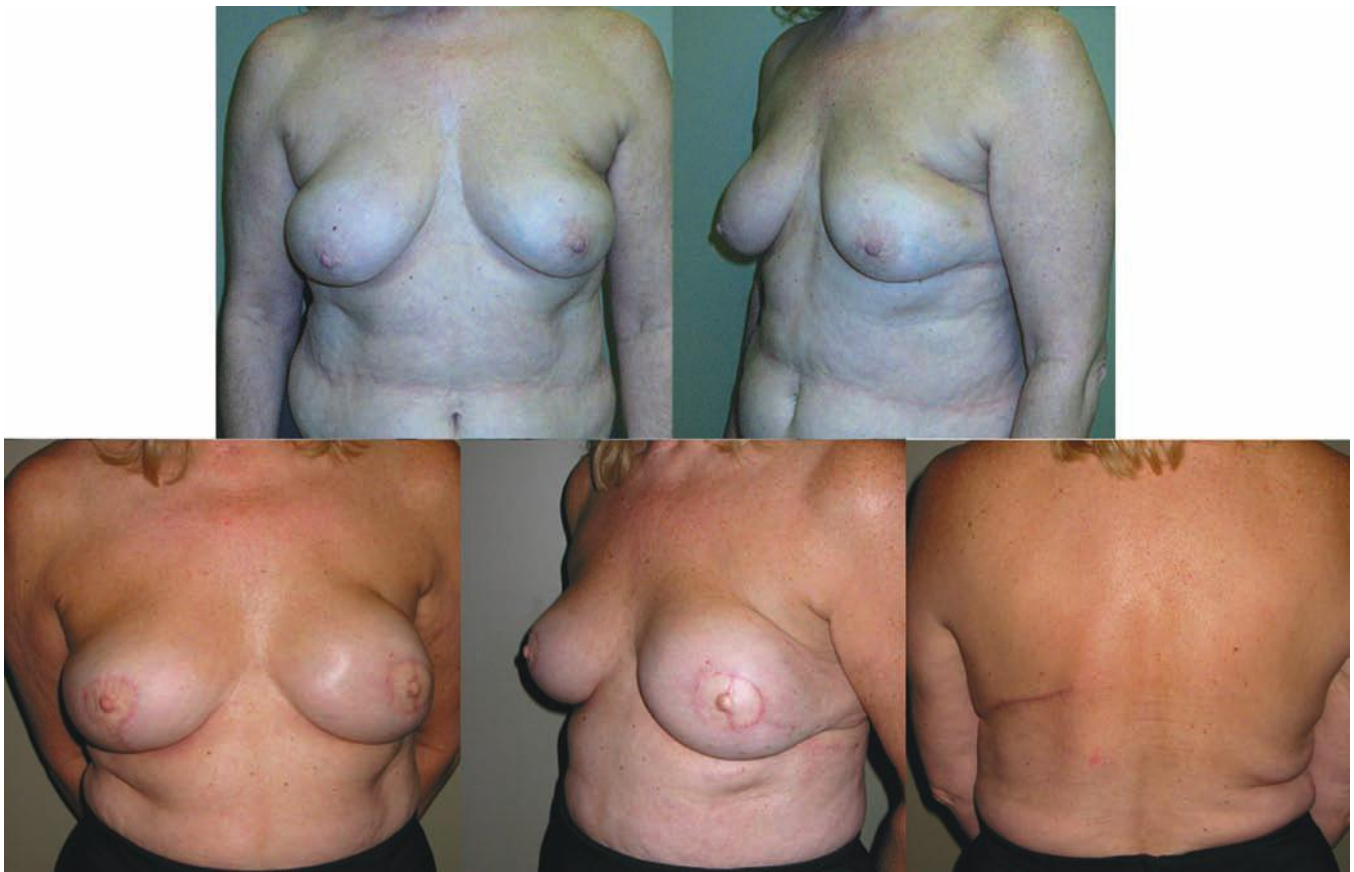


Figure 45-47. Preoperative and postoperative photos of a 58-year-old woman with a left latissimus dorsi flap/silicone implant breast reconstruction and right symmetrization mastopexy. (Photographs reproduced with permission from M. Gimbel.)

intrathoracic dead space infections and as a myocutaneous flap for head and neck reconstruction. Although it is a reliable flap, the loss of the pectoralis major muscle results in upper extremity weakness and cosmetic deformity from loss of the anterior axillary fold.⁵³

The rectus abdominis muscle is a type III axial pattern flap that can be based on the superior epigastric vessels or the deep

inferior epigastric vessels.⁵¹ When elevated as a myocutaneous flap it can be designed with a transverse (TRAM) or vertical rectus abdominis myocutaneous skin paddle. Although the vertical rectus abdominis muscle flap has better vascularized skin due to its multiple longitudinally oriented perforators, the TRAM flap provides a larger area of donor skin that can be primarily closed with an easily concealable scar. The rectus abdominis muscle is frequently used for lower sternum reconstruction when the pectoralis muscle is insufficient. It can also be used in pedicle or free flap configuration for repair of large chest wall defects from cancer resection (Fig. 45-49).

The latissimus dorsi myocutaneous flap is probably the most widely used flap in nonsternal chest wall reconstructions due to its broad size, location, reliability, and pedicle length. The flap is based on the thoracodorsal vessels arising from the subscapular system. Its secondary blood supply comes from the posterior intercostal and lumbar vessels.⁵² The arc of rotation of this flap can extend to most areas on the ipsilateral torso as well as to the abdomen, head and neck, and upper arm. The serratus anterior muscle can be included on the same vascular pedicle to further increase its surface area. Use of this donor site is relatively well tolerated, but shoulder weakness can be significant. The major drawbacks of the latissimus flap are its conspicuous scar and the high risk of seroma.⁵³

The trapezius muscle flap, based on the transverse cervical vessels, is generally used as a pedicled flap to cover the upper midback, base of neck, and shoulder. The superior portion of the muscle along with the acromial attachment and spinal accessory nerve are preserved to maintain shoulder elevation function.

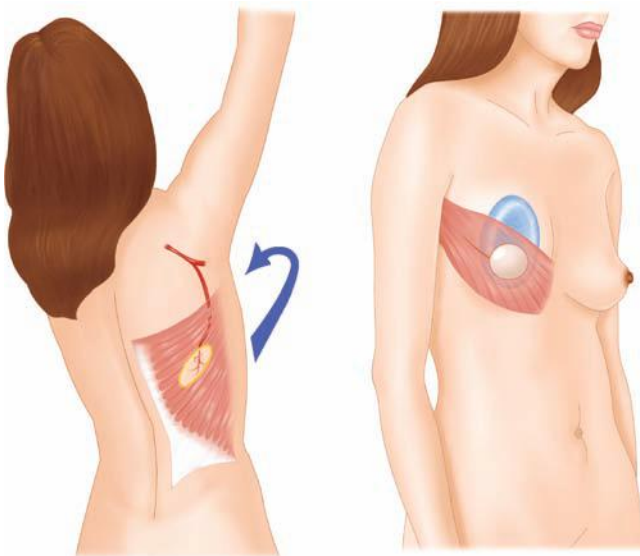


Figure 45-48. Latissimus dorsi flap/implant-based breast reconstruction. (Illustrations reproduced with permission from M. Gimbel.)

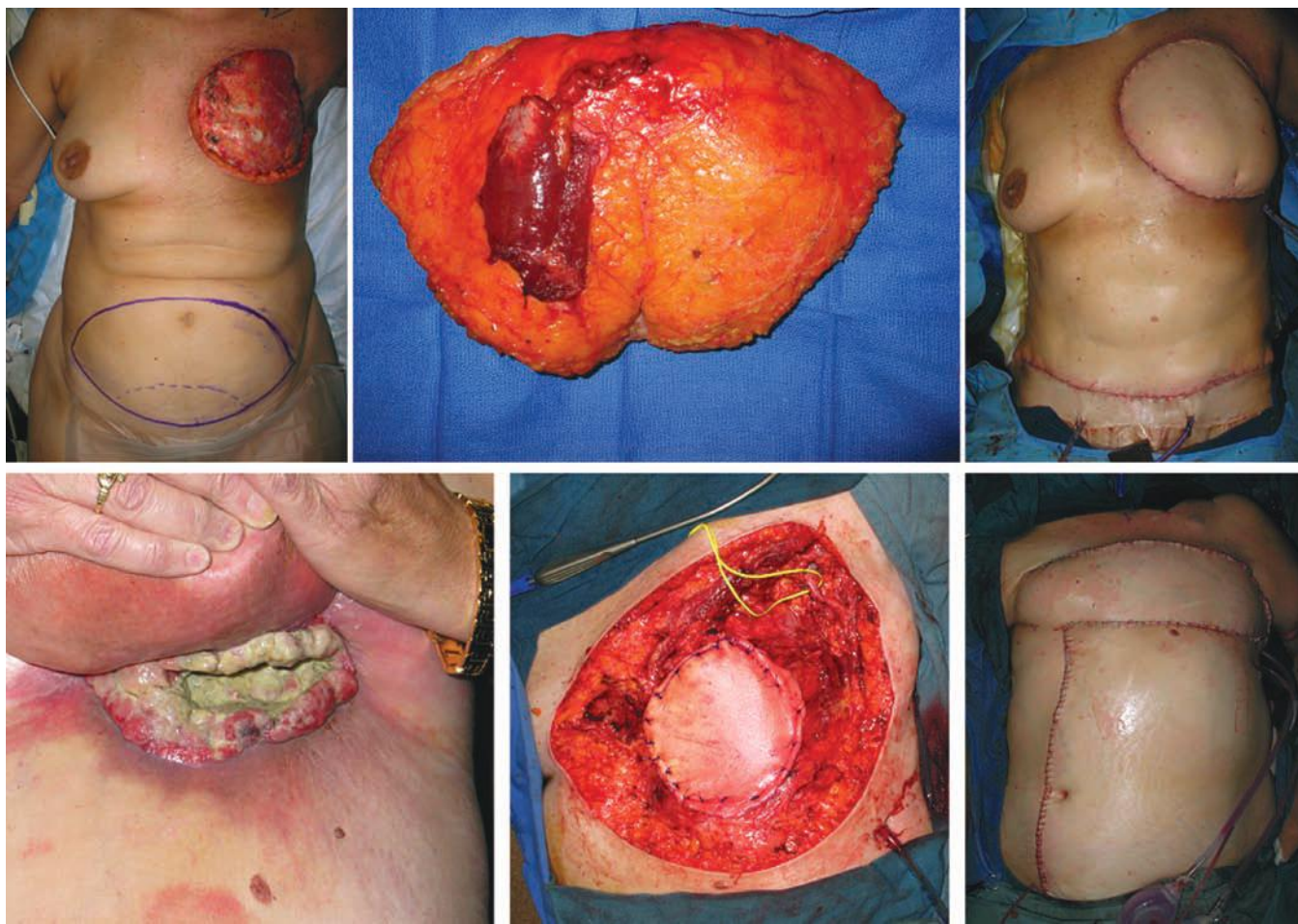


Figure 45-49. *Top row:* Free transverse rectus abdominis muscle reconstruction of a large partial-thickness chest wall defect. *Bottom row:* Full-thickness chest wall defect reconstructed in two layers with human acellular dermal allograft and overlying pedicled vertical rectus abdominis muscle flap. (Photographs reproduced with permission from M. Gimbel.)

Other useful flaps of the thoracic region include the scapular/parascapular fasciocutaneous flap, the external oblique flap, the medially or laterally based thoracoepigastric skin flaps, and the omental flap.

When a full-thickness defect of the chest wall involves more than two adjacent ribs, the inherent rigidity of soft tissue flaps may provide insufficient chest wall integrity. Although cadaveric bone and autologous bone grafts have been used in the past to lend structural support, the availability of well-tolerated synthetic and biologic materials has become more common. These materials include polypropylene (Prolene), polyethylene (Marlex), and polytetrafluoroethylene (Gore-Tex) meshes, methyl methacrylate, and acellular dermal allograft. Even if these avascular foreign bodies must be removed due to chronic infection, often a thick fibrous layer of tissue will have formed that can maintain chest wall stability.⁵³

Abdominal Wall. The abdominal wall also protects the internal vital organs from trauma, but with layers of strong torso-supporting muscles and fascia rather than with osseous structures. The goals of reconstruction are restoration of structural integrity, prevention of visceral eventration, and provision of dynamic muscular support. Defects in the abdominal wall may arise from trauma, oncologic resection, congenital deformities, and infection. By far the most common reason for abdominal wall deficiency, however, is incisional fascial dehiscence

and herniation after laparotomy. When a reconstruction plan is being formulated, careful physical examination and review of the medical history will help prevent selection of an otherwise sound strategy that, because of previous incisions and trauma, is destined for failure.

Partial Defects of the Abdominal Wall. Large defects of the abdominal skin and subcutaneous tissue are usually easily controlled with skin grafts, local advancement flaps, or tissue expansion. Myofascial defects are more difficult to manage. The abdominal wall fascia requires a minimal-tension closure to avoid dehiscence, recurrent incisional hernia formation, or abdominal compartment syndrome.⁵⁴ Prosthetic meshes are frequently used to replace the fascia in clean wounds and in operations that create myofascial defects. When the area of fascial deficiency is contaminated, as in infected mesh reconstructions, enterocutaneous fistulas, or viscus perforations, prosthetic mesh is avoided because of the risk of infection. A delayed reconstruction can be prefaced by inseting a resorbable polyglactin (Vicryl) mesh that will eventually granulate to allow skin grafting. The ensuing hernia is repaired later with prosthetics under cleaner conditions. The separation-of-components procedure has enjoyed much success in closing large midline defects without resorting to mesh. This procedure involves advancement of bilateral myofascial flaps consisting of the anterior rectus fascia/rectus abdominis/internal oblique/transversus abdominis muscle complex.

Mobility of this myofascial unit is created by release of the external oblique muscle at the semilunate line. Midline defects measuring up to 10 cm superiorly, 18 cm centrally, and 8 cm inferiorly can be closed using separation of components.⁵⁵ This technique is less effective in closing lateral defects, for which regional muscle and fascial flaps are usually better suited (rectus abdominis flap, internal oblique flap, external oblique flap).⁵⁴

Full-thickness abdominal defects and large myofascial defects require large robust pedicled flaps or free flaps for closure. The tensor fasciae latae pedicled flap, based on the ascending branch of the lateral circumflex femoral vessels, is useful in reconstructing the lower two-thirds of the abdomen. Bilateral flaps can be used for very large defects, although the skin-grafted donor site is unsightly. The rectus femoris flap and the vastus lateralis flap can be used for smaller lower abdominal defects. The “mutton-chop” flap, which is an extended rectus femoris flap with fascia lata included distally, has been used successfully in closing massive defects.^{56,57} Large defects of the upper abdominal wall may be repaired with pedicled extended latissimus dorsi flaps with attached pregluteal fascia. Very large full-thickness defects, especially superiorly, are best treated with free tissue transfer of large myofascial units such as the latissimus dorsi or the tensor fasciae latae. These can also be innervated flaps to reestablish contractile force and strength in the abdominal wall.

Extremity Reconstruction

Posttraumatic Reconstruction. With the beginnings of modern orthopedic and plastic surgery, improvements in the understanding of anesthesia, trauma resuscitation, infection, and the availability of early antibiotics, the requirement to amputate almost all open (compound) lower extremity fractures as a life-saving procedure gradually decreased while attempts at limb salvage became more realistic. The introduction and maturation of microsurgical techniques witnessed increasing successes in distal extremity replantations and free flap reconstructions. Soft tissue reconstruction thus advanced alongside evolving techniques of bone fixation, joint reconstruction, general vascular surgery, and acute multitrauma management. Current lower extremity reconstruction incorporates the use of vascularized bone, bone distraction techniques, composite tissue flaps, and functioning muscle transfers tailored to the given defect.⁵⁸ The future may behold the use of cadaveric vascularized composite allografts or even tissue-engineered vascularized composite tissue constructs.

Common causes of high-energy lower extremity trauma include road traffic accidents, falls from a height, direct blows, sports injuries, and gunshots. Understanding the anatomy of the lower limb compartments, nerve and vascular supplies, muscle functions, skeletal structure, and mechanics is essential for accurate bony and soft tissue restoration for function and appearance. Several limb-salvage scoring systems have been suggested to aid in the decision regarding whether to amputate or attempt limb salvage, but their routine use remains controversial; nevertheless, they can provide guidance during this life-altering decision process.⁵⁹ Compound fractures are often classified according to the system devised by Gustilo and colleagues (Table 45-12).⁶⁰

In addition to following standard multiple trauma evaluation and resuscitation guidelines, the multidisciplinary team must assess the injured limb for neurovascular status, soft tissue defects and degloving, configuration of fractures, and

Table 45-12

Gustilo and Anderson classification of compound fractures

CLASSIFICATION	DESCRIPTION
Grade I	Wound <1 cm; minimal contamination, comminution, and soft tissue damage
Grade II	Wound >1 cm; moderate soft tissue damage and minimal periosteal stripping
Grade IIIa	Substantial contamination and severe soft tissue damage but adequate fracture coverage; usually due to high-energy trauma
Grade IIIb	Substantial contamination, periosteal stripping, severe soft tissue damage, and inadequate fracture coverage; usually due to high-energy trauma
Grade IIIc	Any open fracture with an associated arterial injury requiring repair

presence of compartment syndrome. Neurovascular status and evidence for compartment syndrome require frequent reassessment, particularly following interventions such as fracture reduction, splintage, and surgery. Bony stabilization may be critical to controlling fracture hemorrhage. Doppler ultrasound examination may help assess vascular integrity. Angiography is a lengthier procedure that provides more detailed information, but the team must be cognizant that delay to revascularization increases the risk of massive reperfusion injury and multiple organ failure.⁶¹ Compartment syndrome must be released with urgent fasciotomies when present. Its most critical early feature is increasingly severe pain especially on passive stretch of the compartment's musculature; pulselessness, pallor, paresthesia, and paralysis are late signs. Compartment pressure monitors are useful in patients who are unconscious or have proximal nerve blocks in place. Antitetanus vaccine and antibiotics should be provided as soon as possible according to contemporary guidelines.⁶² An evaluation of the patient as a whole allows treatment to be planned within the context of comorbidities, socioeconomic considerations, and rehabilitative potential. The loss of plantar sensation historically favored below-knee amputation, but this is no longer an absolute recommendation.⁶¹

With the availability of microvascular free tissue transplantation, radical débridement (i.e., wound excision) can be adequate even for the largest wound. Early one-stage wound coverage and bony reconstruction is generally advocated and should be performed jointly by extremity trauma orthopedic and plastic surgical teams whenever possible.^{61,62} It is reasonable for reconstruction to be deferred briefly if there remain tissues of questionable viability so that these can be reassessed and débrided as required. Placement of a temporary negative pressure dressing between débridements helps reduce bacterial ingress and the inflammatory response. If débridement produces an irregular dead space that cannot be completely obliterated, or if tissues remain questionable even after a second look, the resultant cavity may be filled with antibiotic-impregnated beads or available vascularized soft tissues to act as a spacer

until definitive reconstruction is possible. This applies also to segmental bone losses within a soft tissue envelope of doubtful viability. In these situations, soft tissue coverage preferably is still achieved early; bony reconstruction can be completed at a later date, when both the bone and soft tissue envelope are stable and healthy. It remains debated whether fasciocutaneous or muscular flaps are superior for treating compound fractures. Dead space is critical to obliterate, and this is more readily achieved using muscle. Fasciocutaneous flaps may be superior for coverage of metaphyseal fractures, particularly around the ankle. Reviewed experimental data in animals suggest that diaphyseal tibial fractures with periosteal stripping are better covered by muscle instead of fasciocutaneous flaps.⁶³ Perforator-based chimeric flaps, such as the anterolateral thigh flap with a chimeric portion of vastus lateralis, can be designed to incorporate the best features of both tissue types for the given defect.

Once meticulous débridement is complete, the order of surgical repair is fracture stabilization followed by vascular repair and reconstruction of a stable soft tissue envelope. The choice of method for soft tissue coverage is determined by the location and extent of the injury (Table 45-13). Coverage for weight-bearing areas should be durable, stable (nonshearing), and sensate. Properly fitted footwear provides essential protection against pressure-related complications. Split-thickness skin grafts are reasonable for coverage of exposed healthy muscle or soft tissue. Local flaps may be used to cover smaller defects. Island pedicled perforator-based flaps are more versatile in design and inset, preserve viable muscles by excluding them from flap harvest, and can be a useful option when there is no significant degloving injury (Fig. 45-50). Using retrograde pedicle dissection, they can be harvested in freestyle fashion both to avoid the zone of injury and to suit the defect requirements.⁶⁴ Free tissue transplantation is preferred for larger or more complex defects, particularly in the middle and lower thirds of the leg where there are less soft tissues available for reconstruction. Free flaps need not be limited to providing only soft tissue coverage; incorporation of vascularized bone, such as of fibula or iliac crest, can aid in fracture management.⁶⁵ Chimeric flap configurations can improve flap inset into composite defects. Flow-through designs, such as the anterolateral thigh flow-through free flap, can be used to bridge segmental vascular defects to revascularize the distal extremity.⁶⁶ Muscular flaps can be motor innervated to restore lost muscle functions at the recipient site.⁶⁷ Other techniques such as bone distraction and tissue expansion may be indicated in select circumstances. Traditional cross-leg flaps are almost never used now; they cause complete immobilization and increase the risk of deep vein thrombosis and contracture formation.

Osteomyelitis often complicates inadequately débrided compound leg fractures. Delayed coverage also appears to increase the risk of this dreaded complication. Generous irrigation, débridement, removal of dead bone (even in a segment), expedient antibiotic therapy, and healthy soft tissue coverage are important in both acute compound fracture and established posttraumatic osteomyelitis. Large segmental bone losses can be addressed with microvascular free transplantation of osseous flaps or distraction lengthening.^{61,68}

When limb salvage either is not possible or is not in the best interests of the patient, attention is directed to providing soft tissue stump coverage suitable for weight bearing and allowing ambulation with a properly fitted prosthesis. Ideally, local tissues

Table 45-13

Some lower extremity reconstructive options for soft tissue coverage after fracture

AREA OF DEFECT	RECONSTRUCTIVE OPTIONS
Femur	Sartorius muscle/MC flap (anterior defects) TFL muscle/MC flap (posterior defects) Vastus lateralis/medialis muscle/MC (mid to lower thigh defects) ALT/AMT and posterior thigh fasciocutaneous flap Free osseous flaps (e.g., double-barreled fibula osteoseptocutaneous flap) useful for segmental femur defects
Knee and proximal third of tibia	Gastrocnemius muscle (medial or lateral head, or both) with SSG Island pedicled fasciocutaneous flaps (e.g., distally based anterolateral thigh flap; medial sural artery perforator flap) Free tissue transfer for larger defects
Middle third of tibia	Soleus muscle with SSG Gastrocnemius head(s) with SSG Tibialis anterior muscle “open-book flap” (preserves function) Island pedicled fasciocutaneous flaps (e.g., posterior tibial and peroneal perforator flaps) Free tissue transfer for larger defects
Distal third of tibia	Free tissue transfer usually the first choice Reverse flow sural neurofasciocutaneous flap Island pedicled fasciocutaneous flaps (e.g., posterior tibial and peroneal perforator flaps) Local muscle flaps for smaller defects

ALT = anterolateral thigh; AMT = anteromedial thigh; MC = myocutaneous; SSG = split-thickness skin graft; TFL = tensor fasciae latae.

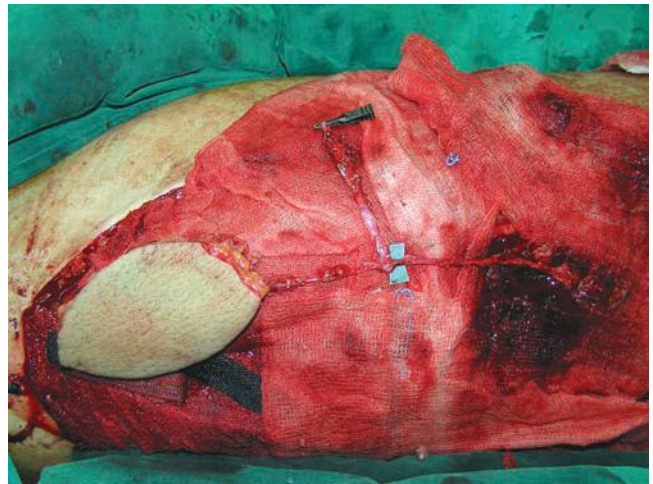
are used; however, when they are unavailable or inadequate, the amputated part can be a useful source of skin grafts or tissues for microvascular free transfers to the stump, which preserves length and avoids a more proximal amputation.

Reconstruction after Oncologic Resection. The refinements in surgical ablation techniques, in adjuvant radiation therapy and chemotherapy, and in limb reconstruction methods have opened the possibility for curative limb-sparing treatments instead of amputation. Extensive soft tissue and segmental long bone defects from radical tumor resection and radiation-compromised wound healing can often be reconstructed now by liberal importation of fresh tissues through microvascular free tissue transplantation tailored to the defect.

Diabetic Ulceration. The pathophysiology of primary diabetic lower limb complications has three main components: peripheral neuropathy (motor, sensory, and autonomic), peripheral vascular disease, and immunodeficiency. Altered foot



A



B



C



D



E



F

Figure 45-50. Perforator-based island pedicled anterolateral thigh flap for soft tissue coverage of the upper third lateral leg. **A.** Soft tissue defect with exposed tibial metaphysis after débridement. Note the arterial hand-held Doppler signal (red dot) around which the flap has been designed. The flap has been reverse-planned and the pivot point determined along the axis of the descending branch of the lateral circumflex femoral artery (black line). **B.** The flap has been harvested and its pedicle skeletonized to maximize freedom of flap motion; note the additional backup vein in case venous supercharge might be required. **C.** Satisfactory flap perfusion following inset. **D.** Flap perfusion became compromised postoperatively but (**E**) improved with bedside maneuvers; if improvement did not occur, backup venous supercharge would have been available. **F.** The regional fasciocutaneous flap has provided durable, color- and texture-matched soft tissues for reconstruction around the knee; importantly, the pliability of the flap tissues has allowed for a full range of knee movement to be maintained. (Photographs reproduced with permission from L. Lin.)

biomechanics and gait caused by painless collapse of ligamentous support, foot joints, and foot arches change weight-bearing patterns. Blunted pain allows cutaneous fissuring and ulceration to progress. Multiflora infections are established amid local immunodeficiency and microvasculopathy. Frank neuroarthropathic Charcot's foot deformities may ultimately result. Cutaneous ulcerations may chronically deteriorate relatively painlessly, involving deeper tissues, including bone. Persistent soft tissue infection and osteomyelitis, worsened by peripheral vascular compromise and immunodeficiency, traditionally ends in gangrene and amputation. More than 60% of nontraumatic lower extremity amputations occur in diabetics.⁶⁹ Indeed, the age-adjusted lower extremity amputation rate in diabetics (5.5 per 1000 diabetics) was approximately 28 times that of people without diabetes (0.2 per 1000 people).⁶⁹ Improved patient education and medical management, timelier detection of diabetic foot problems and referral for treatment, and the use of more refined techniques for wound management play important roles in improving the chances of limb preservation.⁷⁰

Diabetic patients with lower limb disease often have significant multisystemic comorbidities that must be optimized for surgery; strict perioperative control of blood glucose levels is mandatory. Clinical examination must include documentation of sensory deficits, vascular insufficiencies, and evidence of osteomyelitis. Plain radiographs, MRI, nuclear bone scans, and angiography or duplex imaging may be indicated. A patient with significant vascular disease may be a candidate for lower extremity endovascular revascularization or open bypass.⁷¹ Nerve conduction studies may diagnose surgically reversible neuropathies at compressive sites and aid in decisions about whether to perform sensory nerve transfers to restore plantar sensibility.⁷⁰ Antibiotic and fungal therapies should be guided by tissue culture results.

Plastic surgical management starts with thorough débridement of devitalized or infected tissues, purulent cavities, and osteomyelitic bone. Methods of wound closure are dictated by the extent and location of the postdébridement defect (Table 45-14). Vacuum-assisted closure may be appropriate for superficial defects. Skin grafts should be used cautiously and not in weight-bearing areas. Local and regional flaps can be used after careful evaluation of their vascularity given concurrent peripheral vascular disease and possible recent distal vascular bypass procedures. Microvascular free tissue transfers are appropriate when defects are large or when local flaps are not available. Combination lower extremity bypass and free flap coverage has proved beneficial for the treatment of the diabetic foot in terms of healing and reduction of disease progression.⁷² Orthopedic surgeons should be consulted to improve foot biomechanics and address bony prominences to reduce the risk of recurrent ulceration. Proper footwear (including orthotic devices and off-loading shoe inserts), hygiene, and toenail and skin care are essential.⁷⁰

Lymphedema. The lymphatic system provides a high-volume transport mechanism, clearing proteins and lipids from the interstitial space to the systemic vasculature by means of differential pressure gradients. Factors that contribute to circulatory lymphatic flow include segmental lymphangion contractility, skeletal muscle activity, and one-way valves that prevent back-flow.^{73,74} The lymphatics course throughout the body alongside the venous system, into which they eventually drain via the

Table 45-14

Some reconstructive options for the diabetic foot

AREA OF DEFECT	RECONSTRUCTIVE OPTIONS
Forefoot	V-Y advancement Toe island flap Single toe amputation Lisfranc's amputation
Midfoot	V-Y advancement Toe island flap Medial plantar artery flap Free tissue transfer Transmetatarsal amputation
Hindfoot	Lateral calcaneal artery flap Reversed sural artery flap Medial plantar artery flap ± flexor digitorum brevis Abductor hallucis muscle flap Abductor digiti minimi muscle flap Free tissue transfer Syme's amputation
Foot dorsum	Supramalleolar flap Reversed sural artery flap Thinner free flaps (e.g., temporoparietal fascia, radial forearm, groin, thinned anterolateral thigh flaps)

major thoracic and cervical ducts. With lymphatic obstruction, abnormal connections form between the superficial and deep lymphatics and between the lymphatic and venous systems. Lymphatic stagnation, hypertension, and valvular incompetence contribute to edema, inflammatory fibrovascular proliferation, and collagen deposition, causing firm, nonpitting swelling with peau d'orange cutaneous changes. Lymphoscintigraphy reveals the lymphatic anatomy and quantifies lymphatic flow. MRI provides anatomic information regarding lymphatic trunks, nodes, and obstructive lesions. It is essential to rule out neoplastic lymphatic invasion, especially after oncologic ablation, as a cause of secondary lymphedema. Lymphangiosarcoma is a rare cause of lymphedema that is deadly if diagnosed late.⁷⁵

Primary lymphatic obstruction may arise from congenital malformations of the lymphatic system such as lymphatic hypoplasia, functional insufficiency, or absence of lymphatic valves. Identified genetic causes include the autosomal dominant Milroy's disease. Lymphedema praecox accounts for >90% of cases of primary lymphedema, generally appears during puberty but sometimes as late as the third decade, and occurs more commonly in females. It is usually unilateral and limited to the foot and calf. Lymphedema tarda appears after the age of 35 years and is relatively rare. Secondary (acquired) lymphedema is much more common, with filariasis being the leading cause worldwide.⁷⁶ In Western countries, secondary lymphedema is more commonly the result of neoplasms and their surgical treatments and radiotherapy.⁷⁶

The mainstays of management for lower extremity lymphedema are patient education and nonsurgical measures, including one or more of the following: use of external compressive garments and devices, limb elevation, administration of antibiotics for episodes of cellulitis, and specialized complex physical therapy.^{77,78}

Until recently, the efficacy of available surgical options was generally poor, so they were reserved for cases in which aggressive nonsurgical measures had failed. The classic Charles procedure involved radical excision of lymphedematous suprafascial tissues with skin grafting for coverage; cosmetic outcomes were often disastrous, and functional problems arose due to high rates of contracture, wound breakdown, and ulcerations. This method was later modified into multiple staged excisions of subcutaneous tissues. Other techniques include liposuction and bridging procedures.⁷⁸ Microsurgical lymphatic-lymphatic, lymphatic-venous, lymphatic-venous-lymphatic, and lymph node-venous anastomoses were all tried historically, with some techniques showing efficacy early on but long-term results showing high variability.⁷⁹ Recently, however, with an increased understanding of its pathophysiology and improved preoperative investigations, objective staging of lymphedema severity has become more accurate and allowed microsurgeons to tailor treatments for properly selected patients.^{80,81} These factors, alongside improvements in microsurgical techniques, instrumentation, and long-term postoperative care, have provided better surgical results and a resurgence in interest in microsurgical treatment for lymphedema.⁷⁶ Nonsurgical techniques can be, and usually are, combined with any of the surgical methods.

Pressure Sore Treatment

A *pressure ulcer* is defined as tissue injury, usually over a bony prominence, due to pressure or a combination of pressure and shear forces. These wounds occur in patients debilitated by age, illness, immobilization from orthopedic injuries, or spinal cord injury. Prevention of pressure ulcers first requires identification of susceptible patients. Once such patients are identified, measures to prevent development of ulceration include frequent position changes (by both the patient and caretakers), use of pressure reduction equipment (low air loss mattresses and seat cushions, heel protectors), nutritional optimization, hygienic control of incontinence, and medical and/or surgical treatment of muscle spasm and joint contracture. Once an ulcer has developed, these same factors must be carefully evaluated and deficiencies corrected before embarking on a complex reconstructive treatment plan. Successful reconstruction also requires a medically stable, cooperative, motivated patient with adequate social support.

Pressure ulcers are described by their stage, based on depth of tissue injury (Table 45-15).⁸² Stage I and II ulcers are treated

conservatively with dressing changes and basic pressure ulcer prevention strategies as already discussed. Patients with stage III or IV ulcers should be evaluated for surgery. The wound is examined for soft tissue infection or abscess, osteomyelitis, and involvement of deeper structures or spaces (e.g., joint space, urethra, spinal canal) to determine the urgency and specific requirements of the problem. Blood laboratory work and imaging studies are performed to help establish whether soft tissue or bone infection is present. Radiographs are usually adequate to rule out osteomyelitis; CT and MRI are helpful when plain films are equivocal. Wet gangrenous tissue and abscesses should be surgically débrided without delay to prevent or treat sepsis. In patients who do not meet the strict reconstruction criteria, débridement to healthy tissue without subsequent reconstruction may be the optimal treatment. If bone is present at the wound base, it should be débrided only to bleeding bone and left with a smooth contour. Complete ischiectomy should not be performed for ischial decubitus ulcers, because removal of one ischium only transfers subsequent pressure trauma to the contralateral ischium or the perineum. If osteomyelitis is present, which is best proven by culture of specimens obtained by intraoperative bone biopsy, long-term antibiotic therapy guided by microorganism sensitivity is indicated. A special note should be made regarding surgical treatment of spinal cord injury patients with T5 or higher injuries. In these patients, manipulation of a pressure ulcer and even simple urinary retention can trigger autonomic hyperreflexia. This dangerous condition is characterized by critically high blood pressure elevation and sympathetic discharge. Effective management is immediate recognition and reversal of trigger factors along with prompt administration of pharmacologic agents to prevent complications such as intracranial and retinal hemorrhage, seizure, cardiac irregularities, and death.

Direct closure of a pressure ulcer is rarely performed because it usually creates tension in the healing tissues already stressed by nonphysiologic external pressure, predisposing the closure to breakdown. Skin grafting is useful for shallow ulcers with well-vascularized beds that are not subjected to high mechanical shear. Unfortunately, these requirements remove most pressure ulcers from skin graft candidacy. The mainstay of deep pressure ulcer reconstruction is coverage with well-vascularized local flaps. There is debate over whether myocutaneous flaps are better than fasciocutaneous flaps for resurfacing regions prone to excess pressure and shear. Although myocutaneous flaps have excellent bulk and blood supply, muscle has low tolerance for ischemic injury. From an anatomic viewpoint, there is no pressure point on the human body where bone is padded by muscle. On the other hand, although fasciocutaneous flaps provide reasonable bulk and are teleologically appropriate, some argue that subcutaneous fat and fascia have low resistance to pressure and shear forces and have less robust perfusion than muscle.⁸³

The anatomic location of the pressure ulcer naturally has a profound impact on flap choice. Regardless of the wound site, however, the flap design should be very large, more than needed for closure, so that if the ulcer recurs the flap can be readvanced. In addition, care should be taken to place suture lines, the weakest part of the reconstruction, away from pressure points. Over the last few decades, patterns have developed in the selection of particular flaps for particular pressure sores. Sacral decubiti are well treated with gluteus maximus myocutaneous flaps (Fig. 45-51). In ambulatory patients, either the superior or the inferior gluteus muscle is spared to preserve hip extension function. The downside of using the gluteal muscle is the relatively

Table 45-15

National pressure ulcer advisory panel staging system

CLASSIFICATION	DESCRIPTION
Stage I	Intact skin with nonblanchable redness
Stage II	Partial-thickness loss of dermis; may present as blister
Stage III	Full-thickness loss of dermis with visible subcutaneous fat (no deeper structures exposed)
Stage IV	Full-thickness loss of dermis with exposed bone, tendon, or muscle
Unstageable	Full-thickness loss of dermis with ulcer base obscured by eschar



Figure 45-51. Flap reconstruction of pressure ulcers. *Top row:* Preoperative and 1-month postoperative photos of a stage IV sacral decubitus ulcer treated with a myocutaneous gluteus maximus flap. *Bottom row:* Preoperative and 1-month postoperative photos of a stage IV trochanteric ulcer treated with a myocutaneous V-Y tensor fasciae latae flap. (Photographs reproduced with permission from M. Gimbel.)

bloody dissection. A common alternative is the gluteal fasciocutaneous advancement or rotational flap. Ischial pressure sores are generally due to sitting in a wheelchair with improper cushioning or insufficient position changes. A good first-choice flap for ischial wound reconstruction is the hamstring V-Y myocutaneous flap. The gluteus maximus flap may also be transposed inferiorly to cover this wound. A fasciocutaneous alternative is the posterior thigh flap, based on the continuation of the inferior gluteal artery. Trochanteric ulcers develop from prolonged positioning in the lateral decubitus position or from poorly fitting seat or wheelchair equipment. The tensor fasciae latae myocutaneous flap is an expendable muscle unit in ambulatory patients that has a reliable blood supply. It can be advanced superiorly or transposed on its long arc of rotation (see Fig. 45-51). Good second-choice flaps are the rectus femoris muscle flap and the vastus lateralis myocutaneous flap. When pressure sores are neglected, they can become confluent, forming large areas of deep tissue destruction. This dire situation may require hip disarticulation and use of the upper leg soft tissue as a total thigh flap for coverage.

The postoperative care after flap reconstruction of pressure ulcers is as important for success as the surgery itself. The authors recommend transfer of the patient from the operating room table onto an air-fluidized bed, where the patient will remain for the next 7 to 10 days in the hospital. Meticulous instructions must be

given to the nursing staff and therapists regarding the positioning and rolling of the patient to prevent stressing the suture lines during these maneuvers. Nutrition and muscle spasm control are carefully maintained. The posthospitalization care plan, which should have been arranged preoperatively, is confirmed to avoid lapses in proper care. Patients with ischial sores are advised to abstain from sitting for 6 weeks to allow for sufficient healing. Care of the pressure ulcer patient is a labor-intensive process that requires attention to detail by the surgeon, nurses, therapists, caseworkers, and family. Unfortunately, small gaps in care inevitably lead to large gaps in the debilitated patient's integument.

Reconstructive Transplant Surgery

Composite tissue allotransplantation (CTA), such as hand and face transplantation, has become a clinical reality and offers enormous potential for many reconstructive problems, including amputation of extremities. However, as with solid organ transplantation, there remains the issue of allograft rejection. In contrast to visceral organ transplantation, which involves homogeneous tissues, CTA may involve a combination of skin, subcutaneous tissue, nerve, blood vessels, muscle, tendon, and bone, and thus carry the antigenicities of all these tissue types. The basic principles of immunosuppression for solid organ

transplantation have been applied to CTA and include therapy with a variety of combinations of T-cell-depleting agents, monoclonal antibodies, calcineurin inhibitors, antimetabolites, and rapamycin. The complications associated with immunosuppression are well known, including opportunistic infections, metabolic disturbances, and malignancies. Patients selected to undergo CTA, specifically hand transplantation, are young and healthy and therefore more resistant to immunosuppressive side effects than typically less robust solid organ recipients.

As with any surgical procedure, the benefits, success rate, and complications must be understood. Unlike solid organ transplantation, CTA is not a lifesaving procedure. There remains much debate over the risks associated with lifelong administration of potentially dangerous immunosuppressive agents to patients who have no life-threatening illness. The ultimate goal in CTA research is immune tolerance in which the recipient of the allograft remains fully immunocompetent yet does not mount an immunologic response to the transplanted allograft. Accomplishment of this goal would allow the decrease or possible elimination of immunosuppressive medications. If immune tolerance is achieved, CTA clinical applications will broaden dramatically as they become the next frontier in reconstructive surgery⁸⁴ (Fig. 45-52).

AESTHETIC SURGERY

The American Medical Association defines *cosmetic surgery* as “surgery performed to reshape normal structures of the body

5► to improve the patient’s appearance and self-esteem.” *Reconstructive surgery* is performed on structures of the body that are abnormal due to congenital defects, developmental abnormalities, trauma, infection, tumors, or disease. It is generally performed to improve function but may also be done to approximate a normal appearance.⁸⁵ In practical terms, there are both reconstructive and cosmetic elements to almost every plastic surgery case, and the definition of “normal” structure is sometimes unclear. Nevertheless, there are patients for whom it is a priority to make surgical changes to their bodies in the clear absence of a functional deformity. Aesthetic surgery patients present a unique challenge to the plastic surgeon, because the most important outcome parameter is not truly appearance, but patient satisfaction. Optimally, a good cosmetic outcome will be associated with a high level of patient satisfaction. For this to be the case, the plastic surgeon must do a careful analysis of the patient’s motivations for wanting surgery, along with the patient’s goals and expectations. The surgeon must make a reasonable assessment that the improvements that can be achieved through surgery will meet the patient’s expectations. The surgeon must appropriately counsel the patient about the magnitude of the recovery process, the exact location of scars, and potential complications. If complications do occur, the surgeon must manage these in a manner that preserves a positive doctor-patient relationship.

Assessment of Facial Aesthetics

A thorough evaluation of the patient who presents for facial aesthetic surgery should start with elicitation of the patient’s chief complaint, and the examination should be focused on that region. Physical examination of the entire face should note skin quality as well as the presence of redundant skin on the neck, jowls, and eyelids. Depth of the nasolabial folds and the presence of “marionette” lines on the chin should be noted.



Figure 45-52. Hemifacial composite tissue allotransplantation in a rat model. (Photographs reproduced with permission from K. McLean.)

Brow position should be evaluated, along with the distance from brow to hairline. Bulging fat in the lower eyelid region and the presence of a “tear trough” deformity, or deep fold at the lid-cheek junction, should be evaluated. Facial fat atrophy and descent, a hallmark of facial aging, should be noted.

Blepharoplasty and Browlift

Excess skin and adipose deposits of the upper eyelid are approached through an incision based on the supratarsal crease.

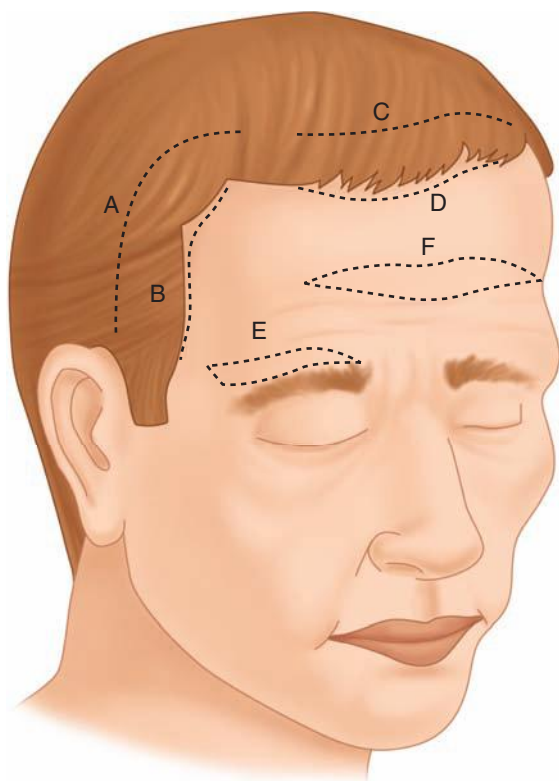


Figure 45-53. Incisions for browlift. A, Temporal scalp incision; B, temporal hairline incision; C, midline scalp incision; D, mid-hairline incision; E, direct eyebrow incision; F, direct forehead incision.

Careful attention to marking will avoid the complication of overresection. A strip of orbicularis muscle is often excised to accentuate the supratarsal fold. Fat deep to the orbital septum is resected selectively. In the lower lid, excess skin is removed through a subciliary incision. Lower eyelid fat may be either excised or repositioned. Complications can include hematoma, lower lid retraction, and injury to ocular muscles. If a hematoma forms in the retro-orbital region, a true surgical emergency exists. Permanent vision loss can occur if it is not immediately decompressed. Brow ptosis, judged relative to the superior orbital rim, can be corrected through a number of incisions (Fig. 45-53).⁸⁶

Facelift

Correction of jowls, nasolabial folds, and redundant neck skin can be accomplished with a facelift procedure that both removes skin and tightens the superficial musculoaponeurotic system (SMAS) layer. The SMAS lies deep to the subcutaneous tissue and contains the muscles of facial expression. The facial nerves are in a plane just deep to the SMAS. The SMAS can be simply plicated or a portion of it excised and closed. A sub-SMAS dissection technique can help to elevate and develop this layer in separate fashion, with care being taken to avoid injury to the underlying facial nerves. The incisions for most facelift techniques are preauricular with extension into the temporal hairline superiorly and into the retroauricular region posteriorly and inferiorly (Figs. 45-54 and 45-55). The platysmal layer is continuous with the SMAS layer and can be plicated through a small neck incision to eliminate the appearance of vertical bands along the muscle edge. The most common facelift complication is hematoma, which may require operative drainage to prevent skin flap necrosis. Injury to facial nerves, most often temporal

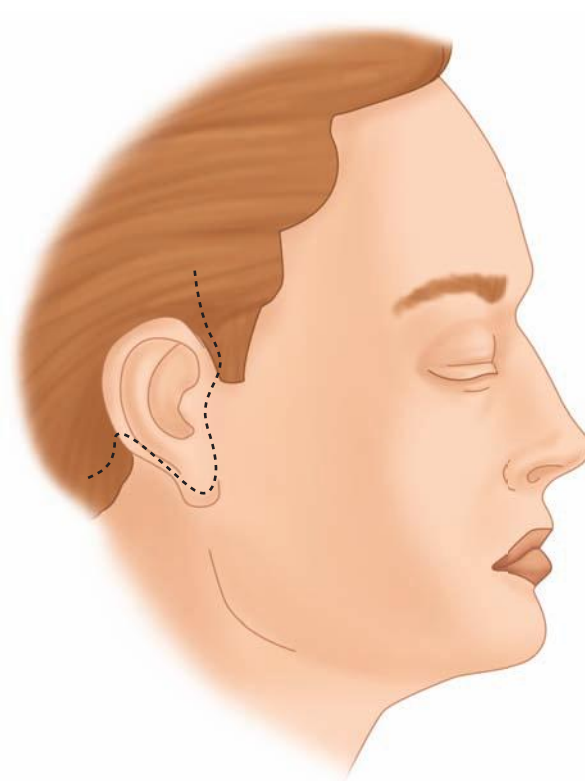


Figure 45-54. Incisions for cervicofacial rhytidectomy.

branch and marginal mandibular branch, is seen in approximately 1% of cases.⁸⁷

Rhinoplasty

The key to understanding rhinoplasty is appreciating the complex nasal anatomy (Fig. 45-56) and the way in which altering this framework will impact the appearance of the nose. Evaluation of the rhinoplasty patient not only should include the aesthetic complaints, but also should consider the function of the nasal airways. Nasal airway obstruction can occur from several structural problems. A deviated septum can severely impede airflow, as can problems with the internal nasal valve. Obstruction at the internal nasal valve, which is the junction of the upper lateral cartilage and septum, can be identified by applying lateral traction on the cheek skin to open the valve and observing whether airflow improves (Cottle sign). Airway obstruction can be addressed surgically at the time of rhinoplasty. Aesthetic deformities of the dorsum of the nose are treated by a combination of osteotomies, which serve to reposition the nasal bones, and rasping of the bone. Aesthetic deformities of the tip of the nose are treated by reducing the width of the lower lateral cartilages and/or sewing the cartilages together to reduce tip width. Small tips can be augmented with cartilage grafts harvested from septum or auricle (Fig. 45-57). Complications of rhinoplasty include induction of new nasal airway obstruction and a variety of aesthetic deformities.⁸⁸

Suction Lipectomy

Liposuction involves the removal of adipose tissue through minimal incisions using a hollow suction cannula. Although the scarring is quite innocuous, a key principle of liposuction is that fat is being removed without skin tightening. Therefore, one relies on the patient's inherent skin elasticity to provide retraction over the treated adipose depot. Assessment of skin tone is

**A****B**

Figure 45-55. Facelift. **A.** Preoperative appearance. **B.** Postoperative appearance.

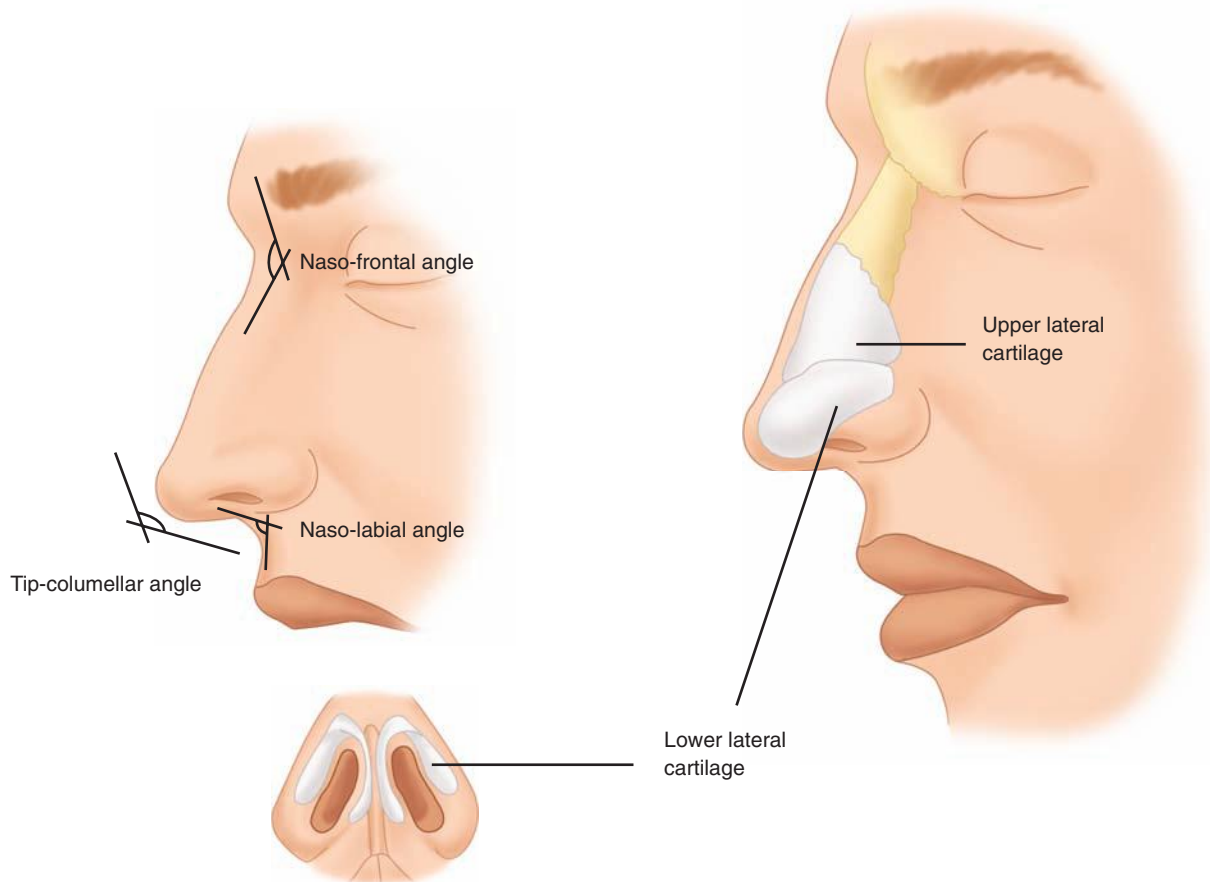


Figure 45-56. Rhinoplasty anatomy.



A



B

Figure 45-57. Rhinoplasty. **A.** Preoperative appearance. **B.** Postoperative appearance.

a vital part of the patient evaluation. If there is skin laxity in the area to be treated, it may worsen after liposuction. Importantly, liposuction should be used as a tool for contouring prominent adipose depots and is not considered a weight loss treatment. The best candidates for liposuction are individuals who are close to their goal weight and have focal adipose deposits that are resistant to diet and exercise (Fig. 45-58). The suction cannula removes fat by avulsing small parcels of adipose tissue into small holes at the cannula tip. With standard suction lipectomy, fat is removed only when the cannula is actively moved through the tissue planes. Minimal tissue effects are seen when the cannula is stationary. In general, larger-diameter cannulas remove adipose tissue at a faster rate but carry a higher risk of causing contour irregularities such as grooving and uneven removal of fat. Newer liposuction technology uses an ultrasonic probe to emulsify the fat via cavitation before suction. Advocates of ultrasonic liposuction report that the technique provides a more even and uniform removal of adipose tissue. Recognizing that no one technique is best for all patients and all anatomic regions, many surgeons use ultrasonic energy selectively.

A major advance in the field of liposuction was the development of tumescent local anesthesia. This method involves the infiltration of very dilute lidocaine and epinephrine (lidocaine 0.05% and epinephrine 1:1,000,000) in large volumes throughout the subcutaneous tissues. Tumescent volumes may range from one to three times the anticipated aspirate volume. The dilute lidocaine provides sufficient anesthesia to allow the liposuction to be performed without additional agents, although many surgeons prefer to use sedation or even general anesthetic when large volumes of fat are to be removed. When general anesthesia is used, the lidocaine dose may be reduced or even eliminated. With tumescent anesthesia, the absorption of the dilute lidocaine from the subcutaneous tissue is very slow, with peak plasma concentrations occurring approximately 10 hours after the procedure.⁸⁹ Therefore, the standard lidocaine dosing limit of 7 mg/kg may be safely exceeded. Current recommendations suggest a limit of 35 mg/kg of lidocaine with tumescent anesthesia.⁹⁰ A very important component of the tumescent anesthetic solution is the dilute epinephrine, which limits blood loss during the procedure.

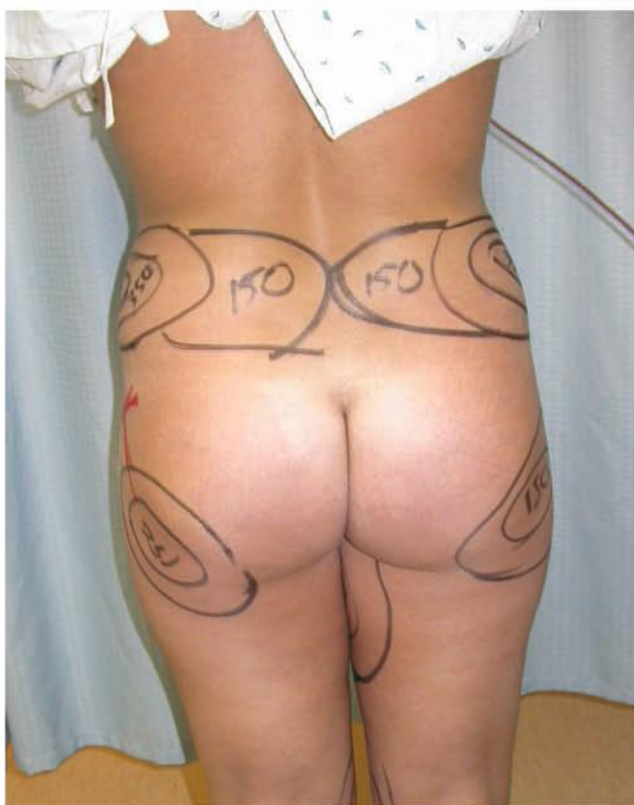
Safety issues are paramount for liposuction because of potential fluid shifts postoperatively and hypothermia. If ≥ 5000 mL of aspirate is to be removed, the procedure should be performed in an accredited acute care hospital facility. After the procedure, vital signs and urinary output should be monitored overnight in an appropriate facility by qualified and competent staff who are familiar with perioperative care of the liposuction patient.⁹⁰

Autologous Fat Grafting

The concept of reinjecting fat tissue harvested by liposuction has been put into practice for decades. Key to the technique is a processing step in which the sterilely collected fat is separated from the aqueous (primarily tumescent fluid) and free lipid fractions. This can be done by centrifugation or filtering. The adipose grafts are then injected into the tissues using specially designed blunt-tipped cannulas. Small aliquots of graft material are injected with each cannula pass, and the fat is interposed within the vascularized tissues of the recipient bed in small channels. Autologous fat grafting has been used primarily for facial aesthetic augmentation of the midface, but has been gaining popularity for breast aesthetic applications, buttock augmentation, and breast reconstruction.



A



B



C

Figure 45-58. A and B. Preoperative photos of a 22-year-old woman with focal adipose deposits on the trunk and extremities. C. Patient 3 months after surgery.

Excisional Body Contouring

When significant skin laxity is present, improvement in contour can be achieved only through skin excision. Therefore, all body-contouring surgery represents a trade of excess skin for scar, and this must be emphasized during patient consultation.

The patient willing to accept scars in exchange for improved contour is likely to be satisfied with the procedures. With the increased number of bariatric surgery procedures over the past decade, body-contouring surgery has become very popular and is emerging as a new subspecialty of plastic surgery.



A



B

Figure 45-59. A. Preoperative photo of 35-year-old woman after gastric bypass and massive weight loss. B. Patient 12 months after a fleur-de-lis abdominoplasty.

Abdominoplasty/Panniculectomy. Abdominoplasty/panniculectomy is the most common body-contouring procedure and can range from a limited-incision skin removal in the lower abdomen to a major skin excision with transposition of the umbilicus and placcation of the rectus muscles to further enhance contour.⁹¹ Some patients may benefit from a concurrent vertical incision to remove skin in two vectors (Fig. 45-59). Possible complications include skin necrosis, persistent paresthesias of the abdominal wall, seroma, and wound separation. Necrosis of the umbilicus may complicate preservation of that structure if the stalk is excessively long or an umbilical hernia is repaired. Adding a vertical resection increases the incidence of skin necrosis, especially at the confluence of scars in the lower abdomen.

Brachioplasty (Arm Lift). Brachioplasty, or arm lift, leaves a visible longitudinal scar on the upper arm. Therefore, it is reserved for patients with excessive skin in that region. The patient willing to accept the scar can be happy with the results. Complications include distal seroma and wound separation. Paresthesias in the upper arm and forearm may occur secondary to injury of sensory nerves passing through the resection area, although this rarely affects function. Scar contracture in the axilla may limit shoulder excursion in rare cases and require revision.

Thigh and Buttock Lift. Treatment of loose skin on the thighs and buttocks involves a spectrum of operations customized to the individual patient. The outer thighs can be lifted at the same time that an abdominoplasty is performed with one continuous

scar along the belt line. The same scar can be continued all the way around the back to lift the buttocks as well. This combination of abdominoplasty, thigh lift, and buttock lift is commonly referred to as a *circumferential lower body lift*. The inner thighs can be contoured by lifting the skin and placing the incisions along the groin crease. Firmly anchoring the deep thigh fascia to Colles' fascia is essential to help prevent spreading of the labia. In cases of severe excess skin on the inner thighs, a long vertical incision is necessary. Complications of thigh and buttock lift include seroma, wound separation, skin necrosis, and change in the shape of the genital region (with possible sexual dysfunction). Blood loss during the procedure may necessitate transfusion.

Reduction Mammoplasty

Breast reduction is performed to treat symptoms of macromastia, most commonly consisting of the triad of upper back pain, bra strap grooving, and rashes under the fold of the breasts. Although this procedure has reconstructive indications, the aesthetic outcome is of considerable importance. Fundamental to the success of the procedure is the establishment of symmetric and proper nipple position. Nipple ptosis is graded by the nipple position relative to the inframammary fold (IMF). Grade 1 ptosis describes a nipple ≤ 1 cm below the IMF. Grade 2 ptosis describes a nipple 1 to 3 cm below the IMF. Grade 3 ptosis describes a nipple position >3 cm below the IMF. *Pseudoptosis* or *bottoming out* is a term used to describe the descent of the breast tissue below the nipple and is a potential long-term complication of breast reduction. In addition to classification of

nipple ptosis, a thorough preoperative evaluation also includes measurement of the distance from sternal notch to nipple bilaterally, as well as measurement of the distance from nipple to IMF. The base width of the breast should also be considered. Many patients are found to have significant baseline asymmetries in these measurements. Preoperative breast cancer screening consistent with current American Cancer Society guidelines should be performed for all patients undergoing elective breast reshaping surgery. The planned new nipple position should be symmetrical

at the IMF along the breast meridian. There are many technical variations of the breast reduction procedure, but nearly all of them have common elements of reshaping the skin envelope in three dimensions and moving the nipple to a new location on a vascularized tissue pedicle. The pedicle is de-epithelialized to preserve the subdermal vascular plexus. Fig. 45-60 shows the classic “keyhole” Wise pattern reduction technique. The skin resection is designed to create a conical shape, and the nipple is transposed on an inferiorly based pedicle.⁹² This results in an inverted T-shaped

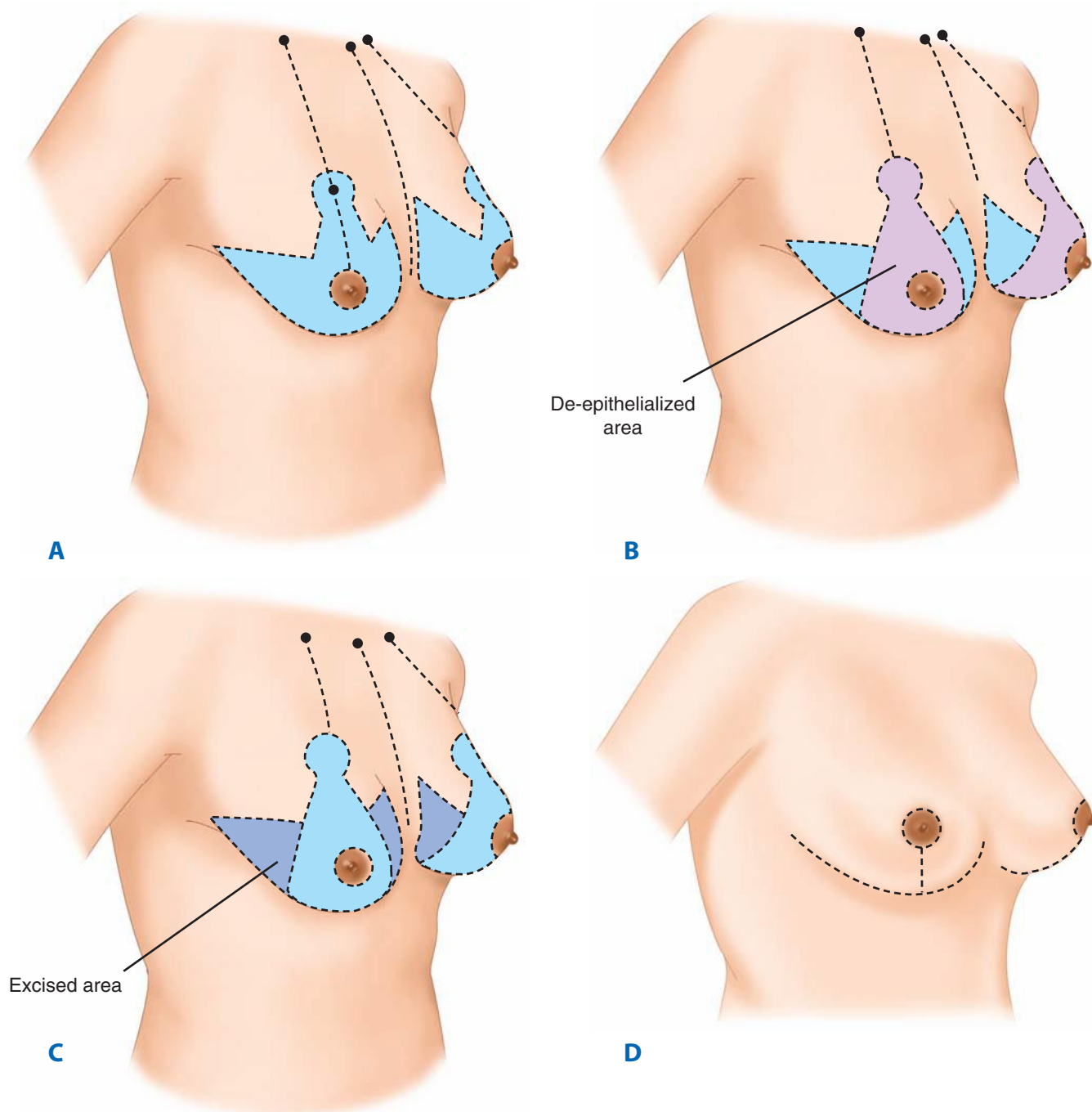


Figure 45-60. Inferior pedicle reduction mammoplasty. **A.** Markings for Wise pattern reduction. **B.** Purple area is region to be de-epithelialized. **C.** Dark blue region is area to be resected. A segment of the inferior pedicle is de-epithelialized. The inferior pedicle is dissected straight down to the chest wall, with maintenance of an 8- to 10-cm pedicle width. Lateral and medial segments are resected. After this is accomplished, the superior flap is dissected to the clavicle. Breast subcutaneous tissue and parenchyma are resected from the superior pole. The vertical limbs are brought together and to the meridian of the inframammary fold. The nipple is then set in its new superior position. **D.** T-shaped incision on final closure.



A



B



C



D

Figure 45-61. A and B. Preoperative photos of a 25-year-old woman with symptoms of upper back pain, bra strap grooving, and rashes under the folds of her breasts treated with a Wise pattern inferior pedicle reduction. C and D. Patient 6 months after surgery.

scar. Fig. 45-61 shows a patient treated using this technique. All breast reduction techniques keep the scars on the lower half of the breast so they are covered by clothing. Techniques have been designed to minimize scar length and even eliminate the horizontal component in the IMF. Fig. 45-62 depicts a vertical scar skin resection pattern with the nipple preserved on a superior pedicle.^{93,94} For excessively large breasts, the required pedicle length may be too long to provide adequate blood supply to the nipple. In such cases, the nipple is removed and replaced onto a viable tissue bed as a full-thickness skin graft. Complications of breast reduction include decreased nipple sensation, nipple loss (rare), skin necrosis, hematoma, and fat necrosis. This last complication can result in a firm mass of scar within the breast that may need careful evaluation and follow-up to distinguish it from a neoplastic mass. Long-term

complications include inability to breastfeed and pseudoptosis, as mentioned earlier.

Mastopexy

In contradistinction to breast reduction, in which patients are treated for symptoms related to heavy breasts, mastopexy is a three-dimensional reshaping of the breast performed with no or minimal volume removal. The principles are the same, however. The skin envelope is contoured, and the nipple location is optimized. Because the degree of ptosis may be less severe than in breast reduction cases, the patterns of skin resection can vary widely. Minimal patterns may involve excision of just a crescent of skin from above the areola or a periareolar (“donut”) resection. The Wise keyhole pattern can be used for larger skin excisions.

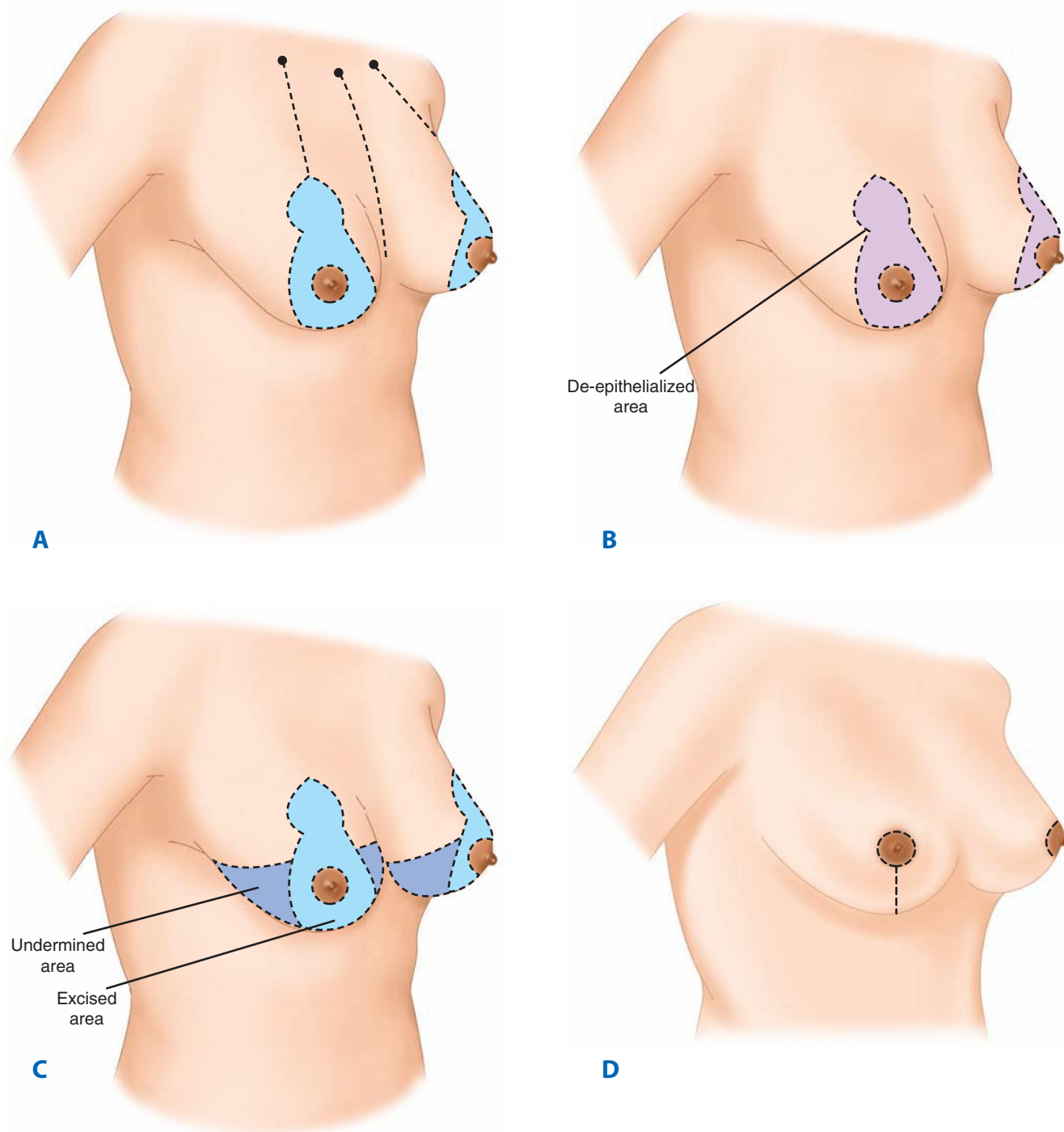


Figure 45-62. Vertical reduction mammoplasty, Lejour technique. **A.** Markings for vertical reduction. **B.** Purple area is region to be de-epithelialized. **C.** Dark blue region represents inferior pole to be resected. The shaded regions are the lateral and medial segments that are to be undermined; these areas can also be liposuctioned. The superior pedicle is de-epithelialized and dissected to the chest wall. The tissue and parenchyma from the inferior pole are resected. The pillars from the lateral and medial segments are sewn together. The nipple is transposed on its pedicle to its new position. **D.** Closure of the vertical mammoplasty. There is bunching up of skin and tissue along the vertical limb that will resolve over time; in addition, the new inframammary fold will declare itself superior to the original one.

Augmentation Mammoplasty

Although the use of prosthetic implants can successfully increase breast size, the surgeon must fully understand both the risks of the biomaterials and the way in which a specific implant of given shape and size can be surgically integrated into the existing breast mound to achieve the desired result.⁹⁵ To address the latter point, the surgeon must first consider

the possible surgical approaches for implant placement. The three commonly used incisions for placement of cosmetic breast implants are inframammary, periareolar, and axillary (Fig. 45-63).⁹⁶ A transumbilical breast augmentation technique has been advocated by some surgeons more recently, but critics of this approach point out that there is poor control over the dissection of the implant pocket and that direct access to the

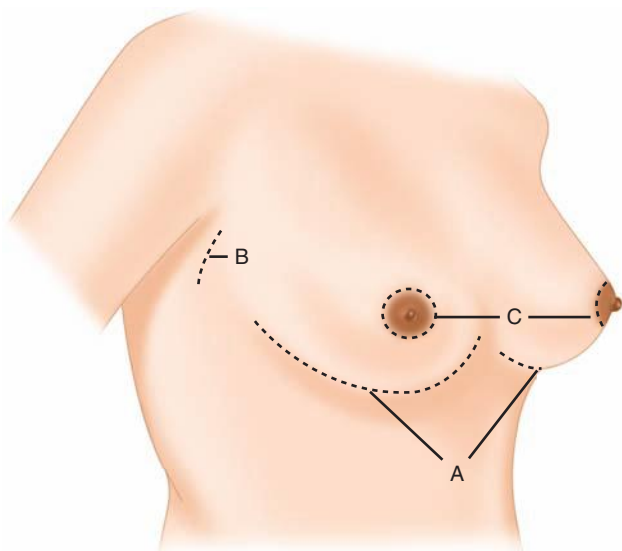


Figure 45-63. Incisions for augmentation mammoplasty. A, Inframammary; B, axillary; C, periareolar.

tissues of the breast is inadequate to control bleeding vessels. In addition, only saline implants can be used with transumbilical breast augmentation because the prefilled silicone implants are too large to pass through the incision and narrow tunnel. The implants may be placed in a subglandular or subpectoral position (Fig. 45-64). Many surgeons prefer the subpectoral placement because it provides greater soft tissue coverage in the upper pole of the breast and can hide contour irregularities related to the implant. This soft tissue coverage is especially important with saline implants, because visible rippling can occur. The next issue to consider is existing nipple position. If a patient has mild ptosis, the sheer volume of the implant may raise the nipple to an acceptable level. For more severe ptosis, a concurrent mastopexy is necessary. Some surgeons advocate performing the mastopexy as a second stage after the implant has settled into position.

Potential complications related to the implant itself are numerous, and the patient must be fully informed of these possibilities before undergoing surgery. One important point is that there is a high likelihood that the patient will require a second

operation to address an implant problem. The implant complications are essentially all local. Although there was concern in the past that implants might be associated with systemic connective tissue disorders, large epidemiologic studies have not supported such a link. The fears over implant safety were so strong that the Food and Drug Administration (FDA) declared a moratorium on the use of silicone gel implants in 1992. At that time, saline-filled implants were still allowed for general cosmetic use. Data were compiled on silicone gel implants, and these devices were approved by the FDA for general use in 2006.⁹⁷ A potential implant complication is rupture of the device. For saline implants, this results in rapid deflation. For silicone gel implants, the rupture may not be obvious and can be confirmed by MRI. Another complication is capsular contracture, which results in a tight envelope of scar that can distort the shape of the implant and cause pain in severe cases. A complication more common to saline devices is the appearance of rippling in the upper pole of the device. Implant malposition can also distort the breast shape and require reoperation. Safety data printed on the official FDA-approved package insert from one of the device manufacturers show the incidence of reoperation to be 29.9% over 7 years in a study of 901 women undergoing primary breast augmentation with saline-filled implants (postapproval study). The rate of severe capsular contracture (grade 3 or 4 on a 4-point scale) was 15.7%, and the rate of implant rupture was 9.8%.⁹⁸ For silicone gel-filled implants, the reoperation rate was observed to be 23.5% over 4 years in a study of 455 women undergoing primary breast augmentation. The rate of severe capsular contracture (grade 3 or 4 on a 4-point scale) was 13.2%, and the rate of implant rupture (evaluated by MRI) was 2.7%. The three most common reasons for operation, in order, were capsular contracture (28.9%), implant malposition (15.6%), and ptosis (14.1%). For secondary augmentation, complication rates were much higher, with the reoperation rate over 4 years rising to 35.2%. The rate of capsular contracture was 17.0%, and the rate of implant rupture was 4.0%.⁹⁹

Another concern regarding breast implants is the issue of whether adequate mammography can be performed after augmentation. Displacement techniques can be used by the mammographer to view the breast tissue. Although patients are advised that implants may affect mammography, a study surveying women who did and did not undergo breast augmentation found no statistical difference in survival or detection of carcinoma between the two cohorts.¹⁰⁰

Gynecomastia

Male breast excess or gynecomastia can be caused by a host of medical diseases and pharmacologic agents. Medical conditions associated with gynecomastia include liver dysfunction, endocrine abnormalities, Klinefelter's syndrome, renal disease, testicular tumors, adrenal or pituitary adenomas, secreting lung carcinomas, and male breast cancer. Causative pharmacologic agents include marijuana, digoxin, spironolactone, cimetidine, theophylline, diazepam, and reserpine. Although these numerous causes must be considered, a majority of patients present with either idiopathic enlargement of the breast parenchyma (more common in teenagers) or simple skin ptosis and excess adipose deposits on the chest wall (considered pseudogynecomastia; more common in adult males). To obtain a flat chest, both liposuction and/or skin excision techniques can be used.¹⁰¹

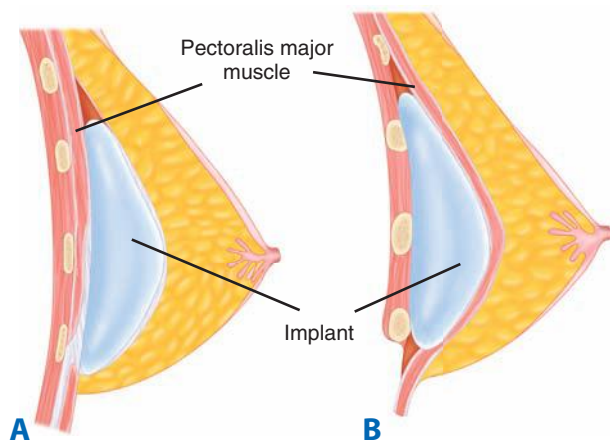


Figure 45-64. Placement of breast implant. A. Subglandular. B. Subpectoral.

Entries highlighted in bright blue are key references.

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46 chapter

Anesthesia for the Surgical Patient

Robert S. Dorian

True Collaboration	1895	Anesthetic Agents	1899	Recovery from Anesthesia	1915
Brief History of Anesthesia	1895	General Anesthesia / 1899		Reversal of Neuromuscular Blockade / 1915	
Modern Beginnings / 1895		Local Anesthetics / 1902		The Postanesthesia Care Unit / 1915	
Ether Day / 1895		Regional Anesthesia: Peripheral vs. Central / 1903		Postoperative Nausea and Vomiting / 1915	
The First Anesthesiologists / 1896		Anesthesia Management	1904	Pain: The Fifth Vital Sign / 1915	
Cocaine: The First Local Anesthetic / 1896		Preoperative Evaluation and Preparation / 1904		Multimodal Analgesia	1916
The Twentieth Century / 1897		Risk Assessment / 1905		The Transversus Abdominis Plane Block	1916
Anesthesiology Today—The Perioperative Physician / 1897		Intraoperative Management	1909	Malignant Hyperthermia	1918
Basic Pharmacology	1897	Induction of Anesthesia / 1909		Future Direction of Anesthesia	1918
Pharmacokinetics / 1897		Management of the Airway / 1910			
Pharmacodynamics / 1898		Fluid Therapy / 1911			
Potency, Efficacy, Lethal Dose, and Therapeutic Index / 1898		Transfusion of Red Blood Cells / 1914			

TRUE COLLABORATION

The discipline of anesthesia embodies control of three great concerns of humankind: consciousness, pain, and movement. The field of anesthesiology combines the administration of anesthesia with the perioperative management of the patient's concerns, pain management, and critical illness. The fields of surgery and anesthesiology are truly collaborative and continue to evolve together, enabling the care of sicker patients and rapid recovery from outpatient and minimally invasive procedures.

BRIEF HISTORY OF ANESTHESIA

The discovery of anesthesia is one of the seminal American contributions to the world. Along with infection control and blood transfusion, anesthesia has enabled surgery to occupy its fundamental place in medicine. Before the advent of modern anesthesia in the 1840s, many substances and methods were tried in the search for pain relief and better operating conditions. Opium, alcohol, exposure to cold, compression of peripheral nerves, constriction of the carotid arteries to produce unconsciousness, and hypnosis (mesmerism) all proved less than satisfactory and dictated rapid and crude surgical procedures. Patients had to be restrained by several attendants, and only the most stoic could tolerate the screams heard in the operating theater. Charles Darwin, who witnessed two such operations, "rushed away before they were completed. Nor did I ever attend again, for hardly any inducement would have been strong enough to make me do so; this being long before the blessed days of chloroform. The two cases fairly haunted me for many a long year."¹

Modern Beginnings

Although Humphrey Davy (1778–1829) suggested using nitrous oxide for the relief of pain in surgical procedures in 1800, this was not pursued until 1844 by dentist Horace Wells (1815–1848). Wells astutely observed that a man who was injured after inhaling nitrous oxide during an exhibition of the "laughing gas" displayed no awareness of pain. After experimenting on himself, Wells attempted to demonstrate the analgesic effects of nitrous oxide for a dental procedure at Harvard Medical School in 1845. The public demonstration was a failure because nitrous oxide has analgesic properties, but does not suffice as the sole anesthetic agent in every patient. Wells never recovered from his humiliating experience and eventually committed suicide. However, he does hold a place in history as the first person to recognize and use the only anesthetic from the 1800s that is still in use today—nitrous oxide.

In 1842, Crawford Long (1815–1878), a physician in rural Georgia, used diethyl ether to induce surgical anesthesia for the removal of two small neck tumors. Diethyl ether had been known for over 800 years but was not used for analgesic purposes. It became an inexpensive and popular recreational drug in the mid-nineteenth century and was used by American medical students at "ether frolics." Although Long did experiments to verify the analgesic effects of ether, he did not publish his work until 1848, in the *Southern Medical Journal*, too late to be the unquestioned discoverer of anesthesia.²

Ether Day

William Morton (1819–1868) was a dentist and partner of Horace Wells. After taking a course in anesthesia from Wells, Morton left the partnership in Hartford, Connecticut, and established himself in Boston. He continued his interest in anesthesia,

Key Points

- 1▶ The incremental interchange of ideas across the specialties of anesthesia and surgery demonstrates the collaborative nature of science in general and medicine in particular. Many surgeons contributed to the growth in anesthesia; more comprehensive anesthesia, in turn, allowed more complex surgery to develop.
- 2▶ The role of the anesthesiologist has expanded to become the perioperative physician. The anesthesiologist evaluates the patient preoperatively, provides the anesthetic, and is involved in postoperative pain relief.
- 3▶ New and improved airway and intubation devices, such as the laryngeal mask airway and the video laryngoscope, along with

the American Society of Anesthesiologists' airway management algorithm, have led to improved management and control of routine and difficult airways.

- 4▶ The specialties of critical care medicine and pain medicine have grown out of the expanded field of anesthesiology. The postanesthesia care unit gave rise to the intensive care unit; the treatment of acute and chronic pain syndromes by anesthesiologists contributed to the growth of pain medicine as a specialty.
- 5▶ The study of proteomics will lead to anesthetics tailored to individuals, maximizing effects and reducing side effects of various anesthetic drugs.

but with diethyl ether replacing nitrous oxide. Ether proved a good choice, as it supports respiration and the cardiovascular system at analgesic levels and is potent enough to administer in room air without hypoxia. He practiced the administration of ether on a dog and then used it when extracting teeth from patients in his office. On October 16, 1846, Morton gave the first public demonstration of ether as an anesthetic for Johns Collins Warren, distinguished surgeon and a founder of Massachusetts General Hospital. In attendance in the surgical amphitheater were several surgeons, medical students, and a newspaper reporter. After anesthesia was induced using a makeshift inhaler, Warren successfully removed a vascular mass from the patient's neck with no ill effects. Warren was an originator of the *Boston Medical and Surgical Journal* (now *The New England Journal of Medicine*), and by November 1846, the demonstration was published in an article by Henry J. Bigelow.³ The stature of Warren and Bigelow lent considerable credence to the advent of surgical anesthesia; as news spread rapidly, surgeons around the world were quick to adopt this "American invention." Massachusetts General Hospital has restored and preserved the original amphitheater where the demonstration took place, now called the *Ether Dome*. It is designated as a Registered National Historic Landmark commemorating the first public demonstration, rather than discovery, of the use of ether as an anesthetic.

The First Anesthesiologists

John Snow (1813–1858) made science out of the art of anesthesia. He was a respected London physician who applied a scholarly, scientific method to investigate the clinical properties and pharmacology of ether, chloroform, and other anesthetic agents. Snow was an astute observer and published a detailed account of the five degrees of etherization in 1847. He vastly improved the apparatus for administering ether and mastered the clinical techniques of anesthetizing patients. As the leading anesthetist of his day, he gave anesthetics to the royal family, including chloroform during labor to Queen Victoria for the birth of Prince Leopold. The Queen's endorsement of "that blessed chloroform" removed the moral and social stigma against relieving pain during childbirth and brought anesthesia into public awareness. Chloroform, popularized in England by James Simpson (1811–1870), had a narrow therapeutic index and placed great clinical demands on the anesthetist. Ether, with its ability to maintain the cardiovascular and respiratory systems, remained in common use in the United States and often was administered by house staff, medical students,

or nurses. Snow encouraged the administration of anesthesia by a physician and felt that a physician dedicated specifically to that purpose was appropriate and necessary. Snow and other exceptional British physicians specializing in anesthesia (Joseph Clover [1825–1882] and Sir Frederick Hewitt [1857–1916]) created a standard of excellence in the latter half of the nineteenth century. This atmosphere of professionalism led to the formation of anesthesia societies and the publication of papers in the prestigious *British Medical Journal* and *The Lancet* in England years before such organizations existed in America.⁴

Cocaine: The First Local Anesthetic

The ancient Incas chewed coca leaves as a stimulant and may have been aware of its local anesthetic properties, allegedly facilitating trephination of the skull by chewing a clump of coca leaves and dripping the resultant saliva into the wound. The active alkaloid of the coca leaf was synthesized in 1860 and called *cocaine* by German chemist Albert Niemann, who noted that it "benumbs the nerves of the tongue, depriving it of feeling."⁵ Sigmund Freud (1856–1939) of Vienna received a supply of cocaine from Merck, studied its properties, and wrote the famous monograph "Über Coca" in 1884. Freud was primarily interested in the stimulant and euphoric effects of cocaine and attempted to use it to treat morphine addiction. Freud and Karl Koller (1857–1944), an ophthalmologic intern, began to perform physiologic experiments with cocaine, measuring its effects on muscle strength. Although they both noted that the drug caused numbness of the tongue when swallowed, it was Koller who first instilled it into his own cornea; report of its use as a local anesthetic galvanized the medical world. Soon after, young American surgeons William Halsted (1852–1922) and Richard Hall described intradermal injection of cocaine and were the first to use it for regional blocks of the facial nerves, brachial plexus, and internal pudendal and posterior tibial nerves.⁶ Halsted later became the first professor of surgery and chief surgeon at Johns Hopkins University, where he remained for more than 30 years. One of the founding fathers of modern surgery, he pioneered radical mastectomy with lymphadenectomy and the use of rubber gloves. While experimenting on themselves, Halsted and other early researchers became addicted to cocaine.⁷ Its toxic effects were the stimulus to find other local anesthetics—procaine was synthesized in 1905 and lidocaine in 1943.

The New York neurologist Leonard Corning (1855–1923) observed the regional blocks of Halsted and Hall, analytically studied local anesthesia effects on dogs, applied his knowledge

to humans, and published the first textbook on local anesthesia in 1886. After experimenting on the spinal nerves of a dog, he intradurally injected a solution of cocaine into a patient, called it *spinal anesthesia*, and commented that it might be useful in surgery. His suggestion went unheeded for more than 10 years, until August Bier (1861–1949), a prominent German surgeon, gave the first deliberate spinal anesthetic.⁸ This incremental interchange of ideas and advances across the Atlantic and across the specialties of anesthesia and surgery demonstrates the collaborative nature of science in general and medicine in particular. The development of surgery and anesthesia exemplifies the dichotomy of two fledgling specialties that are mutually dependent, yet increasingly autonomous.

The Twentieth Century

Developments in anesthesia on both sides of the Atlantic progressed rapidly in the twentieth century. The convergence of technologies that produced the hollow needle and syringe, coupled with the synthesis of barbiturates, gave rise to intravenous (IV) anesthesia in the early 1900s. Barbitol, followed by hexobarbital and thiopental in 1934, produced rapid and more pleasant induction of anesthesia than the inhaled gases. The concept of “balanced anesthesia” began in 1925, when John Lundy (1894–1973) proposed the use of thiopentone for induction, followed by inhaled agents for maintenance of anesthesia. Lundy directed the department of anesthesiology at the Mayo Clinic for 28 years. He established the first recovery room and blood bank, authored the first textbook on modern anesthesia, and helped found the American Board of Anesthesiology.

Nitrous oxide, diethyl ether, and chloroform, all discovered fortuitously by observation, remained the dominant inhalation agents until the accidental discovery of cyclopropane’s anesthetic properties in 1923. Although rapid acting and pleasant smelling, cyclopropane was limited by its flammability and cardiac irritability. Because it was known that fluorination would reduce or eliminate flammability of chemical compounds, British chemist Charles Suckling set out to synthesize an anesthetic that was stable, potent, volatile, and not flammable. He successfully produced halothane in 1953. Introduced into clinical practice in 1956 after extensive testing in Manchester, England, and paired with an accurate calibrated vaporizer, halothane quickly became the most widely used fluorinated anesthetic. Enflurane and isoflurane, synthesized in the United States by Ross Tyrell, were introduced into clinical practice in 1972 and 1981, respectively. The newest agents, desflurane and sevoflurane, were introduced into clinical practice in the early 1990s. They possess a low solubility and are characterized by rapid onset and recovery, making them particularly well suited to outpatient surgery.

The motto of the American Society of Anesthesiologists (ASA) is “Vigilance,” and to that end, there has been continued progress in objective mechanical measurement of patient well-being. The early anesthesiologists used clinical signs such as patient color, depth of respiration, and pulse rate to monitor depth of anesthesia and patient homeostasis. Harvey Cushing, who eventually became Moseley Professor of Surgery at the Peter Bent Brigham Hospital, began the first anesthesia records or “ether charts” in 1895 while a medical student. They recorded pulse, respiratory rates, pupillary diameter, and the amounts of ether and other drugs administered. He later introduced the use of the portable sphygmomanometer of Riva-Rocci to measure blood pressure and the precordial stethoscope to monitor breath

and heart sounds. Monitoring has since progressed to its current state with incremental developments in electrocardiography, pulse oximetry, and mass spectrometry, all mandatory for the safe administration of any anesthetic.

The control of the patient’s airway and respiration as the purview of the anesthesiologist evolved with techniques of endotracheal intubation as pioneered by Sir Ivan Magill (1888–1986) and the invention of the cuffed endotracheal tube by Arthur Guedel (1883–1965). This later merged with the invention of mechanical ventilation and its introduction to the operating room as the embodiment of today’s anesthesia machine. It was this expertise at control of respiration that paved the way for the most revolutionary modern development in anesthesia—the use of muscle relaxants. Curare, a nondepolarizing muscle relaxant, was popularized by Harold Griffith of Montreal. His report of the successful use of curare was a galvanizing event that revolutionized the practice of anesthesia, as the relaxation of abdominal muscles could be controlled to facilitate surgery.⁹ The depolarizing relaxant succinylcholine was introduced in 1949, and research has continued to provide the newer nondepolarizing drugs mivacurium, pancuronium, rocuronium, atracurium, and cisatracurium.

Anesthesiology Today—The Perioperative Physician

The specialty of anesthesia is no longer limited to the operating room. It is natural that anesthesiology, born out of the quest to relieve pain, gave rise to the field of acute and chronic pain medicine. The anesthesiologist consulting on the acute pain service may recommend oral, intramuscular, or IV analgesia with a variety of agents, or patient-controlled analgesia. Postsurgical patients also may be treated with nerve blocks: regional (e.g., brachial plexus, popliteal, and femoral) or neuraxial (epidural or intrathecal). The discipline of chronic pain addresses patients who suffer for months or years with cancer or other debilitating diseases. Treatment modalities escalate from orally administered drugs, to diagnostic and therapeutic nerve blocks, to more invasive measures like dorsal column nerve stimulators and radiofrequency or cryosurgical nerve ablation.

Daily management of the airway, fluids and transfusions, ventilation, drug delivery, monitoring, and caring for the sickest patients in the postanesthesia care unit prepared anesthesiologists to become major contributors to the development of critical care medicine. Of the 28 founding members of the Society of Critical Medicine, 10 were anesthesiologists.¹⁰

The American Board of Anesthesiology became an independent board in 1941 and, since then, has granted board certification to more than 25,000 diplomates. Certificates in Anesthesia Pain Management and Anesthesia Critical Care Medicine are granted to those completing additional postgraduate training. The ASA has more than 35,000 members, and its official journal, *Anesthesiology*, has a monthly circulation of 40,000 worldwide.

BASIC PHARMACOLOGY

Pharmacokinetics

Pharmacokinetics or the *time dependency* of a drug describes the relationship between the dose of a drug and its plasma or tissue concentration. It is what the body does to the drug. It relates to absorption, distribution, metabolism, and elimination. The route of administration, metabolism, protein binding, and

tissue distribution all affect the pharmacokinetics of a particular drug.

Administration, Distribution, Metabolism, and Elimination.

Administration of a drug affects its pharmacokinetics, as there will be different rates of drug entry into the circulation. For example, the oral and IV routes are subject to first-pass effect of the portal circulation; this can be bypassed with the nasal or sublingual route. Other routes of drug administration include transdermal, intramuscular, subcutaneous, or inhalation.

Distribution is the delivery of a drug from the systemic circulation to the tissues. Once a drug has entered the systemic circulation, the rate at which it will enter the tissues depends on several factors:

- Molecular size of the drug, capillary permeability, polarity, and lipid solubility. Small molecules will pass more freely and quickly across cell membranes than large ones, but capillary permeability is variable and results in different diffusion rates. Renal glomerular capillaries are permeable to almost all non-protein-bound drugs; capillaries in the brain are fused (i.e., they have tight junctions) and are relatively impermeable to all but the tiniest molecules (the blood-brain barrier). Un-ionized molecules pass more easily across cell membranes than charged molecules; diffusability also increases with increasing lipid solubility.
- Plasma protein and tissue binding. Many drugs bind to circulating proteins like albumin, glycoproteins, and globulins. Disease, age, and the presence of other drugs will affect the amount of protein binding; drug distribution is affected because only the unbound free portion of the drug can pass across the cell membrane. Drugs also bind reversibly to body tissues; if they bind with high affinity, they are said to be sequestered in that tissue (e.g., heavy metals are sequestered in bone).¹¹
- The fluid volume in which a drug distributes is termed the *volume of distribution* (V_d). This mathematically derived value gives a rough estimation of the overall physical distribution of a drug in the body. A general rule for volume distribution is that the greater the V_d , the greater the diffusability of the drug. Because drugs have variable ionization rates and bind differently to plasma proteins and tissues, the V_d is not a good predictor of the actual concentration of the drug after administration. Determining the apparent V_d (dose/concentration) is an attempt to more accurately ascertain the drug dose administered and its final concentration.

Metabolism is the permanent breakdown of original compounds into smaller metabolites. Drug *elimination* varies widely; some drugs are excreted unchanged by the body, some decompose via plasma enzymes, and some are degraded by organ-based enzymes in the liver. Many drugs rely on multiple pathways for elimination (i.e., metabolized by liver enzymes and then excreted by the kidney).

When a drug is given orally, it reaches the liver via the portal circulation and is partially metabolized before reaching the systemic circulation. This is why an oral dose of a drug often must be much higher than an equally effective IV dose. Some drugs (e.g., nitroglycerine) are hydrolyzed presystemically in the gut wall and must be administered sublingually to achieve an effective concentration.

It is important to remember that the response to drugs varies widely. The disposition of drugs is affected by age; weight;

sex; pregnancy; disease states; and the concomitant use of alcohol, tobacco, and other licit and illicit drugs. Genetic polymorphism, or variations in genes that cause differing drug effects, is another explanation of varying drug response. This will be discussed later in the Future Direction of Anesthesia section on proteomics. This as yet unpredictable response to drugs underscores the importance of the most important monitor in the operating room—the anesthesiologist, who continuously assesses the patient's vital signs and adjusts the doses of anesthetic agents to match the surgical stimulus.

Pharmacodynamics

Pharmacodynamics, or how the plasma concentration of a drug translates into its effect on the body, depends on biologic variability, receptor physiology, and clinical evaluations of the actual drug. It is what the drug does to the body. An *agonist* is a drug that causes a response. A *full agonist* produces the full tissue response, and a *partial agonist* provokes less than the maximum response induced by a full agonist. An antagonist is a drug that does not provoke a response itself, but blocks agonist-mediated responses. An *additive effect* means that a second drug acts with the first drug and will produce an effect that is equal to the algebraic summation of both drugs. A *synergistic effect* means that two drugs interact to produce an effect that is greater than expected from the two drugs' algebraic summation.¹²

Hyporeactivity means a larger than expected dose is required to produce a response, and this effect is termed *tolerance*, *desensitization*, or *tachyphylaxis*. Tolerance usually results from chronic drug exposure, either through enzyme induction (e.g., alcohol) or depletion of neurotransmitters (e.g., cocaine).

Potency, Efficacy, Lethal Dose, and Therapeutic Index

The *potency* of a drug is the dose required to produce a given effect, such as pain relief or a change in heart rate. The average sensitivity to a particular drug can be expressed through the calculation of the effective dose; ED_{50} would have the desired effect in 50% of the general population. The *efficacy* of any therapeutic agent is its power to produce a desired effect. Two drugs may have the same efficacy but different potencies. The difference in potency of the two drugs is described by the ratio $ED_{50}b/ED_{50}a$, where *a* is the less potent drug. If the $ED_{50}b$ equals 4 and the $ED_{50}a$ equals 0.4, then drug *a* is 10 times as potent as drug *b*. For example, 10 mg of morphine produces analgesia equal to that of 1 mg of hydromorphone. They are equally effective, but hydromorphone is 10 times as potent as morphine.

Dose-response curves show the relationship between the dose of a drug administered (or the resulting plasma concentration) and the pharmacologic effect of the drug. The pharmacologic effect might be secretion of a hormone, a change in heart rate, or contraction of a muscle. Between 20% and 80% of the maximum effect, the logarithm of the dose and its response has a linear relationship. The term *dose* only applies to the amount administered and not the actual concentration. If the concentration of an antagonist is increased (in the presence of a fixed concentration of agonist), the dose-response curve will be shifted to the right, and a higher agonist concentration will be required to achieve the desired effect. A basic dose-response curve is shown in Fig. 46-1.

The *lethal dose* (LD_{50}) of a drug produces death in 50% of animals to which it is given. The ratio of the lethal dose and

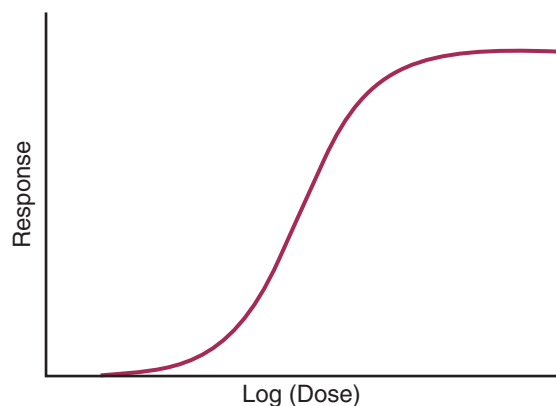


Figure 46-1. Basic dose-response curve.

effective dose, LD_{50}/ED_{50} , is the *therapeutic index*. A drug with a high therapeutic index is safer than a drug with a low or narrow therapeutic index.

ANESTHETIC AGENTS

Anesthesia can be *local*, *regional*, or *general* (Table 46-1). Local anesthesia is accomplished using a local anesthetic drug that can be injected intradermally and is used for the removal of small lesions or to repair traumatic injuries. Local anesthesia is the most frequent anesthetic administered by surgeons and may be accompanied by IV sedation to improve patient comfort.

General Anesthesia

General anesthesia describes a triad of three major and separate effects: unconsciousness (and amnesia), analgesia, and muscle relaxation (see Table 46-1). IV drugs usually produce a single,

Table 46-1

Anesthetic agents, their actions, and their clinical uses

EFFECT	MONITOR	IV DRUGS	POTENT GASES	WEAK GAS	LOCAL ANESTHETICS ^c	
Unconscious (amnesia) (anxiolysis)	EEG and/or clinical signs	Benzodiazepines Midazolam Lorazepam Diazepam Barbiturates Etomidate Ketamine ^a	Sevoflurane Desflurane Isoflurane Enflurane Halothane	Nitrous oxide ^b		
Analgesia	Heart rate Blood pressure Respiratory rate	Opioids Fentanyl Morphine Hydromorphone Nonopioid Ketamine ^a Parecoxib Dexmedetomidine Acetaminophen IV Ketorolac	Sevoflurane Desflurane Isoflurane Enflurane Halothane	Nitrous oxide ^b	Amides Lidocaine Bupivacaine Ropivacaine Prilocaine Mepivacaine	Esters Cocaine Procaine Chloroprocaine Tetracaine Benzocaine
Muscle relaxation (paralysis)	Nerve stimulator	Depolarizer Succinylcholine Nondepolarizers Pancuronium Vecuronium Rocuronium Atracurium	Sevoflurane Desflurane Isoflurane Enflurane Halothane		Peripheral nerve blocks (brachial plexus, femoral, etc.) Central nerve blocks (spinal, epidural)	

EEG = electroencephalogram; IV = intravenous.

^aNote that the IV agents are quite specific in their effects, except for ketamine, which has both amnestic and analgesic qualities.

^bThe potent inhalational anesthetics contribute to all three components of anesthesia, but nitrous oxide has weak amnestic and analgesic properties and provides no muscle relaxation at all.

^cThe local anesthetics produce excellent analgesia and muscle relaxation but contribute nothing to amnesia or anxiolysis; these anesthetics must be supplemented with an IV sedative.

discrete effect, while most inhaled anesthetics produce elements of all three. General anesthesia is achieved with a combination of IV and inhaled drugs, each used to its maximum benefit. The science and art of anesthesia are dynamic processes. As the amount of stimulus to the patient changes during surgery, the patient's vital signs are used as a guide and the quantity of drugs is adjusted, maintaining an equilibrium between stimulus and dose. General anesthesia is what patients commonly think of when they are to be "put under" and can be a cause of considerable preoperative anxiety.¹³

Intravenous Agents

Unconsciousness and Amnesia The IV agents that produce unconsciousness and amnesia are frequently used for the induction of general anesthesia. They include barbiturates, benzodiazepines, propofol, etomidate, and ketamine. Except for ketamine, the following agents have no analgesic properties and do not cause paralysis or muscle relaxation.

Barbiturates The most common barbiturates are thiopental, thiamylal, and methohexital. The mechanism of action is at the γ -aminobutyric acid (GABA) receptor, where they inhibit excitatory synaptic transmission. They produce a rapid, smooth induction within 60 seconds, and wear off in about 5 minutes. In higher doses and in patients with intravascular depletion, they cause hypotension and myocardial depression. The barbiturates are anticonvulsants and protect the brain during neurosurgery by reducing cerebral metabolism.

Propofol Propofol is an alkylated phenol that inhibits synaptic transmission through its effects at the GABA receptor. With a short duration, rapid recovery, and low incidence of nausea and vomiting, it has emerged as the agent of choice for ambulatory and minor general surgery. Additionally, propofol has bronchodilatory properties that make its use attractive in asthmatic patients and smokers. Propofol may cause hypotension and should be used cautiously in patients with suspected hypovolemia and/or coronary artery disease (CAD), the latter of which may not tolerate a sudden drop in blood pressure. It can be used as a continuous infusion for sedation in the intensive care unit setting. Propofol is an irritant and frequently causes pain on injection.

Benzodiazepines The most important uses of the benzodiazepines are for reduction of anxiety and to produce amnesia. Frequently used IV benzodiazepines are diazepam, lorazepam, and midazolam. They all inhibit synaptic transmission at the GABA receptor but have differing durations of action. The benzodiazepines can produce peripheral vasodilatation and hypotension but have minimal effects on respiration when used alone. They must be used with caution when given with opioids; a synergistic reaction causing respiratory depression is common. The benzodiazepines are excellent anticonvulsants and only rarely cause allergic reactions.

Etomidate Etomidate is an imidazole derivative used for IV induction. Its rapid and almost complete hydrolysis to inactive metabolites results in rapid awakening. Like the above IV agents, etomidate acts on the GABA receptor. It has little effect on cardiac output and heart rate, and induction doses usually produce less reduction in blood pressure than that seen with thiopental or propofol. Etomidate is associated with pain on injection and more nausea and vomiting than thiopental or propofol.

Ketamine Ketamine differs from the above IV agents in that it produces analgesia as well as amnesia. Its principal action is on

the *N*-methyl-D-aspartate receptor; it has no action on the GABA receptor. It is a dissociative anesthetic, producing a cataleptic gaze with nystagmus. Patients may associate this with delirium and hallucinations while regaining consciousness. The addition of benzodiazepines has been shown to prevent these side effects. Ketamine can increase heart rate and blood pressure, which may cause myocardial ischemia in patients with CAD. Ketamine is useful in acutely hypovolemic patients to maintain blood pressure via sympathetic stimulation but is a direct myocardial depressant in patients who are catecholamine depleted. Ketamine is a bronchodilator, making it useful for asthmatic patients, and rarely is associated with allergic reactions.

Analgesia. The IV analgesics most frequently used in anesthesia today have little effect on consciousness, amnesia, or muscle relaxation. The most important class is the *opioids*, so called because they were first isolated from opium, with morphine, codeine, meperidine, hydromorphone, and the fentanyl family being the most common. The most important *nonopioid* analgesics are ketamine (discussed earlier in the Ketamine section) and ketorolac, an IV nonsteroidal anti-inflammatory drug (NSAID).

Opioid Analgesics The commonly used opioids—morphine, codeine, oxycodone, meperidine, and the fentanyl-based compounds—act centrally on μ -receptors in the brain and spinal cord. The main side effects of opioids are euphoria, sedation, constipation, and respiratory depression, which also are mediated by the same μ -receptors in a dose-dependent fashion. Although opioids have differing potencies required for effective analgesia, *equianalgesic doses of opioids result in equal degrees of respiratory depression*. Thus, there is no completely safe opioid analgesic. The synthetic opioid fentanyl and its analogues sufentanil, alfentanil, and remifentanil are commonly used in the operating room. They differ pharmacokinetically in their lipid solubility, tissue binding, and elimination profiles and thus have differing potencies and durations of action. Remifentanil is remarkable in that it undergoes rapid hydrolysis that is unaffected by sex, age, weight, or renal or hepatic function, even after prolonged infusion. Recovery is within minutes, but there is little residual postoperative analgesia.

Naloxone and the longer-acting naltrexone are pure opioid *antagonists*. They can be used to reverse the side effects of opioid overdose (e.g., respiratory depression), but the analgesic effects of the opioid also will be reversed.

Nonopioid Analgesics *Ketamine*, an *N*-methyl-D-aspartate receptor antagonist, is a potent analgesic, but is one of the few IV agents that also causes significant sedation and amnesia. Unlike the μ -receptor agonists, ketamine supports respiration. It can be used in combination with opioids, but the dysphoric effects must be masked with the simultaneous use of sedatives, usually a benzodiazepine like midazolam.

Ketorolac is a parenteral NSAID that produces analgesia by reducing prostaglandin formation via inhibition of the enzyme cyclooxygenase (COX). Intraoperative use of ketorolac reduces postoperative need for opioids. Two forms of COX have been identified: COX-1 is responsible for the synthesis of several prostaglandins as well as prostacyclin, which protects gastric mucosa, and thromboxane, which supports platelet function. COX-2 is induced by inflammatory reactions to produce more prostaglandins. Ketorolac (as well as many oral NSAIDs, aspirin, and indomethacin) inhibits both COX-1 and COX-2, which causes the major side effects of gastric bleeding, platelet dysfunction, and hepatic and renal damage.

Parecoxib is a parenteral, predominantly COX-2 NSAID that presumably produces analgesia and reduces inflammation without causing gastrointestinal bleeding or platelet dysfunction.

Dexmedetomidine is an IV α_2 -adrenergic agonist, administered as a continuous infusion, and has sedative and analgesic properties. It is useful for sedation in an intensive care unit setting and as an adjunct to general anesthesia. Side effects are hypotension and bradycardia.

IV *acetaminophen* is an analgesic drug and antipyretic of moderate potency; its site of action is in the central nervous system (CNS), not peripherally. It does not have anti-inflammatory properties and is not considered an NSAID.¹⁴ When used as part of postoperative analgesic therapy, it will reduce the amount of opioids required, reducing side effects (e.g., constipation, sedation, respiratory depression).

Neuromuscular Blocking Agents. Neuromuscular blocking agents have no amnestic, hypnotic, or analgesic properties; patients must be properly anesthetized *before* and *in addition* to the administration of these agents. A paralyzed but unsedated patient will be aware, conscious, and in pain, yet be unable to communicate their predicament. Inappropriate administration of a neuromuscular blocking agent to an awake patient is one of the most traumatic experiences imaginable. Neuromuscular blockade is not a substitute for adequate anesthesia, but is rather an adjunct to the anesthetic. Depth of neuromuscular blockade is best monitored with a nerve stimulator to ensure patient immobility intraoperatively and to confirm a lack of residual paralysis postoperatively.¹⁵

Unlike the local anesthetics, which affect the ability of nerves to conduct impulses, the neuromuscular blockers have no effect on either nerves or muscles, but act primarily on the *neuromuscular junction*.

There is one commonly used *depolarizing* neuromuscular blocker—succinylcholine. This agent binds to acetylcholine receptors on the postjunctional membrane in the neuromuscular junction and causes depolarization of muscle fibers.

Although the rapid onset (<60 seconds) and rapid offset (5–8 minutes) make succinylcholine ideal for management of the airway in certain situations, total body muscle fasciculations can cause postoperative aches and pains, an elevation in serum potassium levels, and an increase in intraocular and intragastric pressure. Its use in patients with burns or traumatic tissue injuries may result in a high enough rise in serum potassium levels to produce arrhythmias and cardiac arrest. Unlike other neuromuscular blocking agents, the effects of succinylcholine cannot be reversed. Succinylcholine is rapidly hydrolyzed by plasma cholinesterase, also referred to as *pseudocholinesterase*.

There are many reasons for a patient to have low pseudocholinesterase levels, such as liver disease, concomitant use of other drugs, pregnancy, and cancer. These factors are usually not clinically problematic, delaying return of motor function only by several minutes. Some patients have a genetic disorder manifesting as atypical plasma cholinesterase; the atypical enzyme has less-than-normal activity, and/or the patient has extremely low levels of the enzyme. The incidence of the homozygous form is approximately 1 in 3000; the effects of a single dose of succinylcholine may last several hours instead of several minutes. Treatment is to keep the patient sedated and unaware he or she is paralyzed, continue mechanical ventilation, test the return of motor function with a peripheral nerve stimulator, and extubate the patient only after he or she has fully regained motor strength. Two separate blood tests must be drawn: *pseudocholinesterase level* to determine the amount of enzyme present, and *dibucaine number*, which indicates the quality of the enzyme. Patients with laboratory-confirmed abnormal pseudocholinesterase levels and/or dibucaine numbers should be counseled to avoid succinylcholine as well as mivacurium, which is also hydrolyzed by pseudocholinesterase. First-degree family members should also be tested. Succinylcholine is the only IV triggering agent of malignant hyperthermia (discussed later in the Malignant Hyperthermia section).

There are several competitive *nondepolarizing* agents available for clinical use. The longest acting is *pancuronium*, which is excreted almost completely unchanged by the kidney. Intermediate-duration neuromuscular blockers include *vecuronium* and *rocuronium*, which are metabolized by both the kidneys and liver, and *atracurium* and *cisatracurium*, which undergo breakdown in plasma known as *Hofmann elimination*. The agent with shortest duration is *mivacurium*, the only nondepolarizer that is metabolized by plasma cholinesterase, and like succinylcholine, is subject to the same prolonged blockade in patients with plasma cholinesterase deficiency. All nondepolarizers reversibly bind to the postsynaptic terminal in the neuromuscular junction and prevent acetylcholine from depolarizing the muscle. Muscle blockade occurs without fasciculation and without the subsequent side effects seen with succinylcholine. The most commonly used agents of this type and their advantages and disadvantages are listed in Table 46-2.

The reversal of neuromuscular blockade is not a true reversal of the drug (as with protamine reversal of heparin) but a reversal of the effect of the neuromuscular blockade. Neuromuscular blocking reversal agents, usually neostigmine, edrophonium, or pyridostigmine, increase acetylcholine levels by inhibiting acetylcholinesterase, the enzyme that breaks

Table 46-2

Advantages and disadvantages to common nondepolarizing neuromuscular blocking agents

AGENT	DURATION (H)	ADVANTAGES	DISADVANTAGES
Pancuronium	>1	No histamine release	Tachycardia; slow onset; long duration
Vecuronium	<1	No cardiovascular effects	Intermediate onset
Rocuronium	<1	Fast onset; no cardiovascular effects	—
Mivacurium	<1	Fast onset; short duration & histamine release	—

Source: Adapted with permission from Rutter TW, Tremper KK. Anesthesiology and pain management. In: Mulholland MW et al, eds. *Greenfield's Surgery: Scientific Principles and Practice*. 4th ed. Philadelphia: Lippincott Williams & Wilkins; 2006:271.

down acetylcholine. The subsequently increased circulating levels of acetylcholine prevail in the competition for the post-synaptic receptor, and motor function returns. Use of the peripheral nerve stimulator is required to follow depth and reversal of motor blockade, but it is essential to correlate data from the nerve stimulator with clinical signs that indicate return of motor function, including tidal volume, vital capacity, hand grip, and 5-second sustained head lift.

Inhalational Agents. Unlike the IV agents, the inhalational agents provide all three characteristics of general anesthesia: unconsciousness, analgesia, and muscle relaxation. However, it would be impractical to use an inhalation-only technique in larger surgical procedures, because the doses required would cause unacceptable side effects, so IV adjuncts such as opioid analgesics and neuromuscular blockers are added to optimize the anesthetic. All inhaled anesthetics display a dose-dependent reduction in mean arterial blood pressure except for nitrous oxide, which maintains or slightly raises the blood pressure. Nitrous oxide, although not potent enough to use alone, provides partial anesthesia and allows a second agent to be used in smaller doses, reducing side effects.

Minimum alveolar concentration (MAC) is a measure of anesthetic potency. It is the ED_{50} of an inhaled agent (i.e., the dose required to block a response to a painful stimulus in 50% of subjects). The higher the MAC, the less potent an agent is. The potency and speed of induction of inhaled agents correlate with their lipid solubility, and this is known as the *Meyer-Overton rule*. Nitrous oxide has a low solubility and is a weak anesthetic agent, but has the most rapid onset and offset. The “potent” gases (e.g., desflurane, sevoflurane, enflurane, and halothane) are more soluble in blood than nitrous oxide and can be given in lower concentrations, but have longer induction and emergence characteristics.

Sevoflurane and desflurane are the two most recently introduced inhalational agents in common use. Because of their relatively lower tissue and blood solubility, induction and recovery are more rapid than with isoflurane or enflurane.

All of the potent inhalational agents (e.g., halothane, isoflurane, enflurane, sevoflurane, and desflurane), as well as the

depolarizing agent succinylcholine, are triggering agents for malignant hyperthermia. Table 46-3 lists the advantages and disadvantages of each agent.

Local Anesthetics

Local anesthetics are divided into two groups based on their chemical structure: the amides and the esters. In general, the amides are metabolized in the liver, and the esters are metabolized by plasma cholinesterases, which yield metabolites with slightly higher allergic potential than the amides (Table 46-4).

Amides. Lidocaine, bupivacaine, mepivacaine, prilocaine, and ropivacaine have in common an amide linkage between a benzene ring and a hydrocarbon chain that, in turn, is attached to a tertiary amine. The benzene ring confers lipid solubility for penetration of nerve membranes, and the tertiary amine attached to the hydrocarbon chain makes these local anesthetics water soluble. Lidocaine has a more rapid onset and is shorter acting than bupivacaine; however, both are widely used for tissue infiltration, regional nerve blocks, and spinal and epidural anesthesia. Ropivacaine is the most recently introduced local anesthetic. It is clinically similar to bupivacaine in that it has a slow onset and a long duration, but is less cardiotoxic. All amides are 95% metabolized in the liver, with 5% excreted unchanged by the kidneys.

Esters. Cocaine, procaine, chlorprocaine, tetracaine, and benzocaine have an ester linkage in place of the amide linkage mentioned earlier in the Amides section. Unique among local anesthetics, cocaine occurs in nature, was the first used clinically, produces vasoconstriction (making it useful for topical application, e.g., for intranasal surgery), releases norepinephrine from nerve terminals resulting in hypertension, and is highly addictive. Cocaine is a Schedule II drug. Procaine, synthesized in 1905 as a nontoxic substitute for cocaine, has a short duration and is used for infiltration. Tetracaine has a long duration and is useful as a spinal anesthetic for lengthy operations. Benzocaine is for topical use only. The esters are hydrolyzed in the blood by pseudocholinesterase. Some of the metabolites have a greater allergic potential than the metabolites of the amide anesthetics, but true allergies to local anesthetics are rare.

Table 46-3

Advantages and disadvantages of common inhalational agents

AGENT	MAC (%)	ADVANTAGES	DISADVANTAGES
Nitrous oxide	105	Analgesia; minimal cardiac and respiratory depression	Sympathetic stimulation; expansion of closed air space
Halothane	0.75	Effective in low concentrations; minimal airway irritability; inexpensive	Cardiac depression and arrhythmia hepatic necrosis; slow elimination
Enflurane	1.68	Muscle relaxation No effect on cardiac rate or rhythm	Strong smell; seizures
Isoflurane	1.15	Muscle relaxation; no effect on cardiac rate or rhythm	Strong smell
Desflurane	6	Rapid induction and emergence	Coughing; high cost
Sevoflurane	1.71	Rapid induction and emergence; pleasant smell; ideal for mask induction	High cost; metabolized by liver

MAC = minimum alveolar concentration.

Source: Adapted with permission from Rutter TW, Tremper KK. Anesthesiology and pain management. In: Mulholland MW et al, eds. *Greenfield's Surgery: Scientific Principles and Practice*. 4th ed. Philadelphia: Lippincott Williams & Wilkins; 2006:270.

Table 46-4

Biologic properties of commonly used local anesthetics

AGENT	EQUIANESTHETIC CONCENTRATION (%)	APPROXIMATE ANESTHETIC DURATION (MIN)	SITE OF METABOLISM
Esters			
Procaine	2	50	Plasma
Chloroprocaine	2	45	Plasma
Tetracaine	0.25	175	Plasma
Amides			
Prilocaine	1	100	Liver/lung
Lidocaine	1	100	Liver
Mepivacaine	1	100	Liver
Bupivacaine	0.25	175	Liver
Ropivacaine	0.3	150	Liver
Etidocaine	0.25	200	Liver

Source: Reproduced with permission from Mather LE, Tucker GT. Properties, absorption, and disposition of local anesthetic agents. In: Cousins MJ, Bridenbaugh PO, eds. *Cousins and Bridenbaugh's Neural Blockade in Clinical Anesthesia and Pain Medicine*. 4th ed. Philadelphia: Lippincott Williams & Wilkins; 2009:49.

The common characteristic of all local anesthetics is a reversible block of the transmission of neural impulses when placed on or near a nerve membrane. Local anesthetics block nerve conduction by stabilizing sodium channels in their closed state, preventing action potentials from propagating along the nerve. The individual local anesthetic agents have different recovery times based on lipid solubility and tissue binding, but return of neural function is spontaneous as the drug is metabolized or removed from the nerve by the vascular system.

Toxicity of local anesthetics results from absorption into the bloodstream or from inadvertent direct intravascular injection. Toxicity manifests first in the more sensitive CNS and then the cardiovascular system.

Central Nervous System Toxicity. As plasma concentration of local anesthetic rises, symptoms progress from restlessness to complaints of tinnitus. Slurred speech, seizures, and unconsciousness follow. Cessation of the seizure via administration of a benzodiazepine or thiopental and maintenance of the airway are the immediate treatment. If the seizure persists, the trachea must be intubated with a cuffed endotracheal tube to guard against pulmonary aspiration of stomach contents.

Cardiovascular System Toxicity. With increasingly elevated plasma levels of local anesthetics, progression to hypotension, increased P-R intervals, bradycardia, and cardiac arrest may occur. Bupivacaine is more cardiotoxic than other local anesthetics. It has a direct effect on ventricular muscle, and because it is more lipid soluble than lidocaine, it binds tightly to sodium channels (it is called the *fast-in, slow-out local anesthetic*). Patients who have received an inadvertent intravascular injection of bupivacaine have experienced profound hypotension, ventricular tachycardia and fibrillation, and complete atrioventricular heart block that is extremely refractory to treatment. The toxic dose of lidocaine is approximately 5 mg/kg; that of bupivacaine is approximately 3 mg/kg.

Calculation of the toxic dose before injection is imperative. It is helpful to remember that for any drug or solution,

1% = 10 mg/mL. For a 50-kg person, the toxic dose of bupivacaine would be approximately 3 mg/kg, or $3 \times 50 = 150$ mg. A 0.5% solution of bupivacaine is 5 mg/mL, so $150 \text{ mL} / 5 \text{ mg/mL} = 30 \text{ mL}$ as the upper limit for infiltration. For lidocaine in the same patient, the calculation is $50 \text{ kg} \times 5 \text{ mg/mL} = 250 \text{ mg}$ toxic dose. If a 1% solution is used, the allowed amount would be $250 \text{ mg} / 10 \text{ mg/mL} = 25 \text{ mL}$.

Additives to Local Anesthetics. Epinephrine has one physiologic and several clinical effects when added to local anesthetics. Epinephrine is a vasoconstrictor, and by reducing local bleeding, molecules of the local anesthetic remain in proximity to the nerve for a longer time period. Onset of the nerve block is faster, the quality of the block is improved, the duration is longer, and less local anesthetic will be absorbed into the bloodstream, thereby reducing toxicity. Although epinephrine 1:200,000 (5 g/mL) added to a local anesthetic for infiltration will greatly lengthen the time of analgesia, epinephrine-containing solutions should not be injected into body parts with end-arteries, such as toes or fingers, as vasoconstriction may lead to ischemia or loss of a digit. When added to the local anesthetic, sodium bicarbonate will raise the pH, favoring the nonionized uncharged form of the molecule. This speeds the onset of the block, especially in local anesthetics that are mixed with epinephrine. The pH of such solutions is around 4.5; therefore, the addition of sodium bicarbonate results in a relatively large increase in pH.¹⁶

Regional Anesthesia: Peripheral vs. Central

Peripheral Nerve Blocks. Local anesthetic can be injected *peripherally*, near a large nerve or plexus, to provide anesthesia to a larger region of the body. Examples include the brachial plexus for surgery of the arm or hand, blockade of the femoral and sciatic nerves for surgery of the lower extremity, ankle block for surgery of the foot or toes, intercostal block for analgesia of the thorax postoperatively, or blockade of the cervical plexus, which is ideal for carotid endarterectomy. Risks of peripheral regional nerve blocks are dependent on their location.

For example, nerve blocks injected into the neck risk puncture of the carotid or vertebral arteries, intercostal nerves are in close proximity to the vascular bundle and have a high rate of absorption of local anesthetic, and nerve blocks of the thorax run the risk of causing pneumothorax. All peripheral nerve blocks may be supplemented intraoperatively with IV sedation and/or analgesics.

Central Nerve Blocks: Spinal and Epidural. Local anesthetic injected *centrally* near the spinal cord—spinal or epidural anesthesia—provides anesthesia for the lower half of the body. This is especially useful for genitourinary, gynecologic, inguinal hernia, or lower extremity procedures. Spinal and epidural anesthesia block the spinal nerves as they exit the spinal cord. Spinal nerves are mixed nerves; they contain motor, sensory, and sympathetic components. The subsequent block will cause sensory anesthesia, loss of motor function, and blockade of the sympathetic nerves from the level of the anesthetic distally to the lower extremities. Subsequent vasodilation of the vasculature from sympathetic block may result in hypotension, which is treatable with IV fluids and/or pressors.

Spinal Anesthesia Local anesthetic is injected directly into the dural sac surrounding the spinal cord. The level of injection is usually below L1 to L2, where the spinal cord ends in most adults. Because the local anesthetic is injected directly into the cerebrospinal fluid surrounding the spinal cord, only a small dose is needed, the onset of anesthesia is rapid, and the blockade is thorough. Lidocaine, bupivacaine, and tetracaine are commonly used agents of differing durations; the block wears off naturally via drug uptake by the cerebrospinal fluid, bloodstream, or diffusion into fat. Epinephrine as an additive to the local anesthetic will significantly prolong the blockade.

Possible complications include hypotension, especially if the patient is not adequately prehydrated; high spinal block requires immediate airway management; and postdural puncture headache sometimes occurs. Spinal headache is related to the diameter and configuration of the spinal needle and can be reduced to approximately 1% with the use of a small 25- or 27-gauge needle.

Cauda equina syndrome is injury to the nerves emanating distal to the spinal cord resulting in bowel and bladder dysfunction and lower extremity sensory and motor loss. It has mainly been seen in cases in which indwelling spinal microcatheters and high (5%) concentrations of lidocaine were used. Indwelling spinal catheters are no longer used.

Epidural Anesthesia Epidural anesthesia could also be called *extradural anesthesia*, because local anesthetics are injected into the epidural space surrounding the dural sac of the spinal cord. Much greater volumes of anesthetic are required than with spinal anesthesia, and the onset of the block is longer—10 to 15 minutes. As in spinal anesthesia, local anesthetic bathes the

spinal nerves as they exit the dura; the patient achieves analgesia from the sensory block, muscle relaxation from blockade of the motor nerves, and hypotension from blockade of the sympathetic nerves as they exit the spinal cord. Note that regional anesthesia, whether peripheral or central, provides only two of the three major components of anesthesia—analgesia and muscle relaxation. Anxiolysis, amnesia, or sedation must be attained by supplemental IV administration of other drugs (e.g., the benzodiazepines or propofol infusion).

Complications are similar to those of spinal anesthesia. Inadvertent injection of local anesthetic into a dural tear will result in a high block, manifesting as unconsciousness, severe hypotension, and respiratory paralysis requiring immediate aggressive hemodynamic management and control of the airway. Indwelling catheters are often placed through introducers into the epidural space, allowing an intermittent or continuous technique, as opposed to the single-shot method of spinal anesthesia. By necessity, the epidural-introducing needles are of a much larger diameter (17- or 18-gauge) than spinal needles, and accidental dural puncture more often results in a severe headache that may last up to 10 days if left untreated.

ANESTHESIA MANAGEMENT

Preoperative Evaluation and Preparation

The ASA has adopted basic standards for the evaluation of patients before surgery. These standards require the anesthesiologist to determine the medical status of the patient by developing a plan of anesthetic care and to discuss this plan with the patient and/or legal guardian.

The preoperative visit results in a summary of all pertinent findings, including a detailed medical history, current drug therapy, complete physical examination, and laboratory and specific testing results. Based on these findings, the anesthesiologist may find that the patient is not in optimal medical condition to undergo elective surgery. These findings and opinions are then discussed with the patient’s primary physician, and the surgery may be delayed or cancelled until the patient’s medical condition is further tested and optimized.

The detailed medical history obtained at the preoperative visit should include the patient’s previous exposure and experience with anesthesia, as well as any family history of problems with anesthesia. History of atopy (medication, foods, or environmental) is an important aspect of this evaluation in that it may predispose patients to form antibodies against antigens that may be represented by agents administered during the perioperative period. A careful review of major organ systems and their function also should be performed.

The physical examination is targeted primarily at the CNS, cardiovascular system, lungs, and upper airway. Specific areas to investigate are shown in Table 46-5.

Table 46-5			
Preoperative physical examination			
CENTRAL NERVOUS SYSTEM	CARDIOVASCULAR SYSTEM	RESPIRATORY SYSTEM	ORAL AIRWAY
Consciousness; neurocognition; peripheral sensory	Blood pressure; standing and sitting, bilateral; peripheral pulses; heart auscultation; heart rate; murmur; rhythm	Auscultation of lungs; wheezes; rales	Cervical spine mobility; visualize uvula; artificial teeth; thyromental distance

Concurrent medications must be fully explored, and adverse interactions with agents administered during the perioperative period need to be considered. However, concurrent medications that produce desired effects (i.e., β -blockade, anti-hypertensive, and antiasthma medications) can and should be continued throughout the perioperative period; patients should be counseled to continue these medications up to and including the morning of surgery. Careful documentation will allow the anesthesiologist to make informed decisions about the perioperative selection of drugs and therapy as well as monitoring techniques.

Preoperative laboratory data and specific testing for elective surgery should be patient and situation specific. Examples include serum potassium for a patient on diuretics, glucose in a diabetic patient, or hemoglobin concentration in any surgery with a high risk of blood loss. Coagulation tests are not necessary if the patient is not receiving anticoagulants or has no signs or symptoms of abnormal clotting. Otherwise healthy patients usually do not need preoperative laboratory testing, and tests performed within the previous 6 months are usually sufficient.¹⁷ Other tests that should be generated by history and physical examination include chest radiograph if there is evidence of chest disease and pulmonary function tests in patients who are morbidly obese, severe asthmatics, or patients undergoing pulmonary resection surgery. An electrocardiogram should be performed in all symptomatic patients and in asymptomatic men age 45 years or older and asymptomatic women age 50 years or older. Urine pregnancy testing should be performed on the day of surgery in all women of childbearing age.

Risk Assessment

An integral part of the preoperative visit is for the anesthesiologist to assess patient risk. Risk assessment encompasses two major questions: (a) Is the patient in optimal medical condition for surgery? and (b) Are the anticipated benefits of surgery greater than the surgical and anesthetic risks associated with the procedure?

Research into quantifying preoperative factors that correlate with the development of postoperative morbidity and mortality has recently gained great interest. Originally designed as a simple classification of a patient's physical status immediately before surgery, the ASA physical status scale is one of the few prospective scales that correlate with the risk of anesthesia and surgery (Table 46-6).

Criticism of the ASA scale is primarily due to its exclusion of age and difficulty of intubation (discussed later in

Table 46-7

American Society of Anesthesiologists physical status and mortality

SCORE	MORTALITY (%)
P1	0.1
P2	0.2
P3	1.8
P4	7.8
P5	9.4

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this chapter). Cullen and associates examined 1095 patients undergoing total hip replacement, prostatectomy, or cholecystectomy, and found that both age and ASA scale accurately predict postoperative morbidity and mortality¹⁸ (Table 46-7). The ASA scale remains useful and should be applied to all patients during the preoperative visit.

Evaluation of the Airway. The airway examination is an effort to identify those patients in whom management of the airway and conventional endotracheal intubation may be difficult. It is vitally important to recognize such patients before administering medications that induce apnea.

Mallampati Classification. The amount of the posterior pharynx one can visualize preoperatively is important and correlates with the difficulty of intubation. A large tongue (relative to the size of the mouth) that also interferes with visualization of the larynx on laryngoscopy will obscure visualization of the pharynx. The Mallampati classification (Fig. 46-2, Table 46-8) is based on the structures visualized with maximal mouth opening and tongue protrusion in the sitting position.

Other predictors of difficult intubation include obesity, immobility of the neck, interincisor distance <4 cm in an adult, a large overbite, or the inability to shift the lower incisors in front of the upper incisors. The thyromental distance (i.e., the distance from the thyroid cartilage to the mentum [tip of the chin]) should be >6.5 to 7 cm.

Consideration of Patients with Comorbidities. A thorough knowledge of the pathophysiology of concurrent medical conditions regardless of the reason for surgery is essential for optimal perioperative care. Optimal anesthesia extends beyond pharmacology and technical procedures. Specifically, ischemic heart disease, renal dysfunction, pulmonary disease, metabolic and endocrine disorders, CNS diseases, and diseases of the liver and biliary tract can have major impact on the management of anesthesia.

Ischemic Heart Disease. Ischemic heart disease is the result of the heart demanding more oxygen (O_2) than its supply can provide. A supply problem may be due to many factors, including hypoxia, anemia, hypotension and coronary artery atherosclerosis, thrombosis, or spasm. Additionally, the problem may be an increase in myocardial O_2 demand (tachycardia). In the vast majority of cases, the most responsible lesion is a reduction in the luminal area of coronary arteries due to atherosclerosis.

Table 46-6

American Society of Anesthesiologists physical status classification system

P1 A normal healthy patient
P2 A patient with mild systemic disease
P3 A patient with severe systemic disease
P4 A patient with severe systemic disease that is a constant threat to life
P5 A moribund patient who is not expected to survive without the operation
P6 A declared brain-dead patient whose organs are being removed for donor purposes



MALLAMPATI CLASSIFICATION

- CLASS 1: Soft palate, fauces, uvula, pillars
 CLASS 2: Soft palate, fauces, portion of uvula
 CLASS 3: Soft palate, base of uvula
 CLASS 4: Hard palate only

Figure 46-2. The Mallampati classification.

An estimated 14 million people in the United States have ischemic heart disease. Of these, as many as 4 million have few or no symptoms and are unaware that they are at risk for angina pectoris, myocardial infarction, or sudden death.

An important goal of the preoperative visit is for the anesthesiologist to ascertain the patient's severity, progression, and functional limitations induced by ischemic heart disease. Furthermore, this visit can elucidate the possibility of previously undiagnosed ischemic heart disease. A thorough investigation of risk factors for ischemic heart disease is essential during the preoperative visit. The risk of perioperative death due to myocardial infarction in patients without ischemic heart disease is approximately 1%.¹⁹ In contrast, the risk in patients with known or suspected ischemic heart disease is approximately 3%,¹⁹ and in patients undergoing surgery for peripheral vascular disease, the combined risk of death due to cardiac causes is 29%.²⁰

Major Risk Factors for Coronary Artery Disease. The risk of *hypercholesterolemia* is proportional to the increased serum level of low-density lipoprotein cholesterol. Reduction achieved via decreased dietary fat or pharmacotherapy reduces risk.

Hyperlipidemia may be familial and thus may account for the fact that a strong family history of premature CAD is a significant risk factor. High-density lipoprotein cholesterol is protective.

Although definitely a risk factor, hypertension alone probably does not cause plaques. Rather, it may act synergistically with hypercholesterolemia by first causing mechanical wall stress and damage.

Smoking causes endothelial damage, and therefore promotes plaque thrombosis. Cessation greatly reduces the risk of CAD.

Diabetes mellitus is a strong independent risk factor. A hypothesis is that glycosylation products cause release of growth factors that stimulate smooth muscle proliferation.

Other Risk Factors. *Hyperhomocysteinemia* is becoming an established independent risk factor, but is still under evaluation. Reduction of levels by folate therapy may be beneficial.

Advanced age, male sex, obesity, and a sedentary life-style can also put a person at risk for developing ischemic heart disease.²¹

Drugs used for the medical management of patients with ischemic heart disease should be continued throughout the perioperative period. Withdrawal of an antihypertensive drug or suspension of β -blockade can induce unwanted increases in sympathetic nervous system activity.¹² Induction of anesthesia in patients with ischemic heart disease can be safely accomplished with a number of IV drugs. As many as 45% of patients have been shown to have myocardial ischemia during the stress of tracheal intubation, and direct laryngoscopy should be used for the shortest time possible to minimize the magnitude of stimulation.²²

The intraoperative anesthetic technique should allow for the prompt control of hemodynamic variables; the maintenance of the balance between myocardial O_2 delivery and myocardial O_2 demand is probably the single most important factor in managing patients with ischemic heart disease. In this regard, muscle relaxants with minimal to no effects on heart rate and blood pressure, such as vecuronium and rocuronium, are attractive choices for neuromuscular blockade. Additionally, controlled myocardial depression using a volatile anesthetic in patients with a normal left ventricular ejection fraction may help to minimize the stimulation of the sympathetic nervous system and subsequent increases in myocardial O_2 requirements. In patients with impaired left ventricular function, continued myocardial depression with volatile anesthetics may not be tolerated; the addition of short-acting opioids such as fentanyl is beneficial. In cardiac surgical patients, it is not uncommon for high-dose opioids to be used as the predominant anesthetic.

Pulmonary Disease. Chronic pulmonary disease has developed into a worldwide public health problem. Chronic obstructive

Table 46-8

Mallampati classification

- Class I: soft palate, fauces, uvula, pillars
 Class II: soft palate, fauces, portion of uvula
 Class III: soft palate, base of uvula
 Class IV: hard palate only

pulmonary disease (COPD), distinguished from asthma, which is characterized by reversible airway smooth muscle constriction, is a progressive disease that leads to the destruction of the lung parenchyma.

Infection, noxious particles, and gases can exacerbate COPD. Historically, certain lung function parameters (i.e., significantly abnormal spirometry or arterial blood gas analysis) were once considered contraindications for anesthesia. However, anesthetic techniques have improved, and it has been shown that patients with severe lung disease can safely undergo anesthesia.²³ Zollinger and Pasch found no specific parameters of lung function that were predictive of postoperative lung complications. The highest predictive parameter found was upper abdominal surgery and thoracic surgery.²⁴

General anesthesia can be performed safely in patients with pulmonary disease.²⁵ Inhaled anesthetics are often used due to their bronchodilating properties.²⁶ Some authors have advocated pretreatment with salbutamol, a long-acting β -agonist, which may prevent bronchoconstriction during anesthetic induction.^{27,28}

Regional and local anesthesia have the benefit of avoiding tracheal irritation and stimulating bronchospasm. However, patients with COPD may become hypoxic while lying strictly supine, and sensory levels of anesthetic above T10 are associated with the impairment of respiratory muscle activity necessary for patients with COPD to maintain adequate ventilation.¹²

Intraoperatively, mechanical ventilation using a slow breathing rate (at eight breaths per minute) should be used to allow for passive exhalation in the presence of increased airway resistance. This slow breathing, facilitated by high inspiratory flow rate, may allow for improved maintenance of normal partial pressure of arterial oxygen (PaO_2) and partial pressure of arterial carbon dioxide (CO_2) levels. Patients should also be well hydrated during the procedure with adequate crystalloid/colloid volume therapy, which may allow for less viscous pulmonary secretions following surgery.

Renal Disease. Five percent of the adult population may have pre-existing renal disease that could contribute to perioperative morbidity.²⁹ In addition, the risk of acute renal failure is increased by certain events or patient characteristics independent of pre-existing renal disease, such as hypovolemia and obstructive vascular disease. Ischemic tubular damage (i.e., acute tubular necrosis) is the most likely cause of acute renal failure in the perioperative period, reflecting events that cause an imbalance of O_2 supply to O_2 demand in the medullary ascending tubular cells.

Virtually all anesthetic drugs and techniques are associated with decreases in renal blood flow, the glomerular filtration rate, and urine output, reflecting multiple mechanisms such as decreased cardiac output, altered autonomic nervous system activity, neuroendocrine changes, and positive pressure ventilation. Renal blood flow (15%–25% of the cardiac output) far exceeds renal O_2 needs, but ensures optimal clearance of wastes and drugs. Prehydration and the depth of anesthesia may influence the renal response to anesthesia.

Management of anesthesia in patients with chronic renal disease requires attention to intraoperative fluid management and tight control of ventilation, as respiratory alkalosis will shift the oxyhemoglobin dissociation curve, and respiratory acidosis could raise serum potassium to dangerous levels. Because of

decreased excretion by the kidney, doses of opioids and neuromuscular blocking agents must be attenuated.

Hepatobiliary Disease. Management of anesthesia for the patient with liver disease requires an understanding of the many physiologic functions of the liver: synthesis of albumin and coagulation factors, metabolism of drugs, glucose homeostasis, and the production of bilirubin. Data from the 1970s suggested that approximately 1 in every 700 adult patients who are scheduled for elective surgical procedures has unknown liver disease or is in the prodromal phase of viral hepatitis. Severe hepatic necrosis following surgery and anesthesia is most often due to decreased hepatic O_2 delivery rather than the anesthetic.

Regional anesthesia may be useful in patients with advanced liver disease, assuming coagulation status is acceptable. When general anesthesia is selected, administration of modest doses of volatile anesthetics with or without nitrous oxide or fentanyl often is recommended. Selection of nondepolarizing muscle relaxants should consider clearance mechanisms for these drugs. For example, patients with hepatic cirrhosis may be hypersensitive to mivacurium because of the lowered plasma cholinesterase activity. Perfusion to the liver is maintained by administering fluids (guided by filling pressures) and maintaining adequate systemic pressure and cardiac output.

The coexisting presence of liver disease may influence the selection of volatile anesthetics. Halothane is the anesthetic most studied regarding possible hepatotoxicity. Halothane hepatitis occurs rarely (approximately 1:25,000 patients) and may have an immune-mediated mechanism stimulated by repeated exposures to halothane.³⁰ Halothane, enflurane, isoflurane, and desflurane all yield a reactive oxidative trifluoroacetyl halide and may be cross-reactive, but the magnitude of metabolism of the volatile anesthetics is a probable factor in the ability to cause hepatitis.³¹ Halothane is metabolized 20%, enflurane 2%, isoflurane 0.2%, and desflurane 0.02%; desflurane probably has the least potential for liver injury. Sevoflurane does not yield any trifluoroacetylated metabolites and is unlikely to cause hepatitis. An estimated 15 to 20 million adults in the United States have biliary tract disease. Treatment of gallbladder disease by open or laparoscopic cholecystectomy is most often performed with general anesthesia supplemented with muscle relaxants. Complete biliary tract obstruction could interfere with the clearance of some muscle relaxants dependent on liver metabolism, such as vecuronium and pancuronium. Anesthetic considerations for laparoscopic cholecystectomy are similar to those for other laparoscopic procedures. Insufflation of the abdominal cavity with CO_2 results in increased intra-abdominal pressure that may interfere with the ease of ventilation and venous return. During laparoscopic cholecystectomy, placement of the patient in the reverse Trendelenburg position favors movement of abdominal contents away from the operative site and may improve ventilation. However, this position may further interfere with venous return and reduce cardiac output, emphasizing the need to maintain intravascular fluid volume. Mechanical ventilation of the lungs is recommended to ensure adequate ventilation in the presence of increased intra-abdominal pressure and to offset the effects of systemic absorption of CO_2 used during insufflation of the abdominal cavity. High intra-abdominal pressure may increase the risk of passive reflux of gastric contents. Tracheal intubation with a cuffed tube is advised to minimize the risk of pulmonary aspiration.

Metabolic and Endocrine Disease. Metabolic and endocrine disorders encompass a wide range of diseases. These diseases may be the primary reason for surgery or can exist in patients requiring surgery for other unrelated disorders. Preoperative evaluation of endocrine function consists of relevant medical history, glucose or protein in the urine, vital signs, history of fluctuations in body weight, survey of sexual function, and concomitant medications. The three metabolic and endocrine conditions that are most prevalent in patients undergoing surgery are diabetes mellitus, hypothyroidism, and obesity. The prevalence of all three conditions, either alone or in combination, in the general population has been steadily rising throughout the world for the past 20 to 30 years.^{12,32} The aging population and changes in the diagnostic criteria for diabetes mellitus are sure to continue this trend.^{12,33}

Patients with diabetes are at an increased risk for perioperative myocardial ischemia, stroke, renal dysfunction or failure, and increased mortality.³⁴ Increased wound infections and impairment of wound healing also are associated with the pre-existence of diabetes in patients undergoing surgery.³⁵

The stress response to surgery is associated with hyperglycemia in nondiabetic patients due to increased secretion of catabolic hormones and a combination of reduced insulin secretion and increased insulin resistance.^{36,37} Improved glycemic control in diabetic patients undergoing major surgery has been shown to improve perioperative morbidity and mortality; avoidance of hypoglycemia and hyperglycemic events is the standard of care in these patients.^{33, 38-40}

Anesthetic techniques in the diabetic patient can modulate the secretion of catabolic hormones.⁴¹ However, regional anesthesia may carry greater risks to the diabetic patient with autonomic neuropathy, and the hypotension associated with regional anesthesia may be deleterious to the diabetic patient with coexisting CAD.³³ There is no evidence that regional anesthesia or general anesthesia, either alone or in combination, offers any benefit to the diabetic surgical patient in terms of morbidity or mortality.³³

Hypothyroidism is a deficiency in the secretion of the thyroid hormones, thyroxine and 3,5',3-triiodothyronine, by the thyroid gland. More than 5 million Americans have this common medical condition, and as many as 10% of women may have some degree of thyroid hormone deficiency. Controlled clinical trials have not shown an increase in risk when patients with mild to moderate hypothyroidism undergo surgery.⁴² Nevertheless, close monitoring of these patients for adverse effects of anesthesia, including delayed gastric emptying, adrenal insufficiency, and hypovolemia, is warranted.⁴³

The prevalence of significant obesity continues to rise both in developed and developing countries and is associated with an increased incidence of a wide spectrum of medical and surgical pathologies⁴⁴ (Table 46-9). In the United States, one-third of people have a body weight more than 20% above their ideal weight.⁴⁵ Body mass index (BMI) is calculated by dividing the weight in kilograms by the square of the height in meters. In the United States, the prevalence of a BMI >25 kg/m² is 59.4% for men, 50.7% for women, and 54.9% for adults overall. Patients with a BMI >28 kg/m² have increased perioperative morbidity over the general population.

Anesthetic management of the obese patient is problematic, and tasks such as establishing IV access, applying monitoring equipment, managing the airway, and transporting the patient are more difficult. Ventilation may be a particular

Table 46-9

Disease conditions associated with obesity

CATEGORY	EXAMPLES
Cardiovascular disease	Sudden death, cardiomyopathy, hypertension, coronary artery disease, peripheral vascular disease
Respiratory disease	Restrictive lung disease, sleep apnea
Endocrine disease	Diabetes mellitus, hypothyroidism
GI disease	Hernia, gallstones
Malignancy	Breast, prostate, colorectal cancer
Musculoskeletal	Osteoarthritis, back pain

Source: Reproduced with permission from Adams JP, Murphy PG. Obesity in anaesthesia and intensive care. *Br J Anaesth.* 2000;85:91. By permission of Oxford University Press.

problem because of obstructive sleep apnea or because obesity itself imposes a restrictive ventilatory state with decreased expiratory reserve and vital capacity.¹² Induction of anesthesia is particularly challenging in the obese patient, as there is increased risk of pulmonary aspiration, and the increased mass of soft tissue about the head and neck makes establishing and maintaining a patent airway difficult.

The impact of obesity on the pharmacokinetics of anesthetic drugs is variable. For example, blood volume is often increased in obese patients, which can decrease predicted concentrations of drugs, but adipose tissue has low blood flow, which could elevate blood concentrations of these agents. It is prudent to calculate the first dose of anesthetic based on ideal body weight and to base subsequent dosages on the patient's responsiveness.^{12,46}

Central Nervous System Disease. Diseases of the CNS present unique situations for the anesthesiologist and require an understanding of the relationship between intracranial pressure (ICP), cerebral blood flow (CBF), and cerebral metabolic rate of O₂ consumption (CMRO₂). Preoperative assessment of ICP is difficult, as symptoms of headache, nausea, and vomiting are nonspecific, and signs of retinal changes do not occur acutely. A midline shift on computed tomography scanning or magnetic resonance imaging may indicate an expanding lesion in the brain.

Provision of anesthesia for intracranial procedures must balance hemodynamic factors such as fluid volume, mean arterial pressure, ICP, and CBF. For intracranial tumors, the mass effect of the tumor makes control of ICP and CBF critical. In intracranial aneurysm surgery, the goal of the anesthetic is to prevent sudden increases in systemic blood pressure that could rupture the aneurysm, especially during the stress of laryngoscopy and endotracheal intubation. The relationship between mean arterial pressure, ICP, and CBF is affected by pharmacologic agents. Inhalational agents in high concentrations (>0.6 MAC) cause dilation of the cerebral vasculature, decreasing cerebral vascular resistance. CBF is therefore increased in a dose-dependent fashion, despite decreases in CMRO₂.¹²

Propofol decreases CBF, ICP, and $CMRO_2$.⁴⁷ Propofol may also decrease systemic blood pressure, resulting in a decrease in cerebral perfusion pressure; however, propofol does not alter the autoregulation of CBF.⁴⁸ Etomidate is a potent cerebral vasoconstrictor that reduces CBF and ICP and should be used with caution in patients with epilepsy due to its excitatory effects seen on electroencephalograms.⁴⁹

Opioids decrease CBF and may also decrease ICP under certain conditions. However, Sperry and associates have reported increases in ICP with the administration of fentanyl in head trauma patients.⁵⁰ Additionally, opioids have a depressant effect on consciousness and ventilation that may increase ICP if accompanied by an increase in partial pressure of arterial CO_2 ; opioids should be used with caution in head trauma patients.

Regardless of the drugs or technique selected, maintenance of stable hemodynamics is optimal. Recovery from anesthesia should be smooth, avoiding pain, coughing, and straining, all of which can increase blood pressure and ICP and cause bleeding at the surgical site.

Fluid therapy can increase cerebral edema and ICP when administered in large quantities, resulting in hypervolemia. Euvolemia should be the goal in head trauma patients, whereas hypervolemia may be beneficial for patients with intracranial aneurysms to reduce vasospasm.

INTRAOPERATIVE MANAGEMENT

Induction of Anesthesia

During induction of anesthesia, the patient becomes unconscious and rapidly apneic, myocardial function is usually depressed, and vascular tone abruptly changes. The induction of general anesthesia is the most critical component of practicing anesthesia, as the majority of catastrophic anesthetic complications occur during this phase. There are several different techniques used for the induction of general anesthesia, each with significant advantages and disadvantages (Fig. 46-3). Each patient

must be carefully evaluated during the preoperative period to ensure that the most efficacious and safe technique is used.

IV induction, used primarily in adults, is smooth and is associated with a high level of patient satisfaction. The addition of opioids will blunt the response of laryngoscopy and intubation to avoid hypertension and tachycardia.

In a patient with a full stomach, the standard induction technique may result in vomiting and pulmonary aspiration of stomach contents. The goal of *rapid sequence induction* is to achieve secure protection of the airway with a cuffed endotracheal tube while preventing vomiting and aspiration.

Rapid sequence induction is performed as follows:

- Proceed only after evaluation of the airway predicts an uncomplicated intubation.
- Preoxygenate the patient.
- Rapidly introduce an IV induction agent (e.g., propofol).
- An assistant to the anesthesiologist presses firmly down on the cricoid cartilage to block any gastric contents from being regurgitated into the trachea, a muscle relaxant is injected, and the trachea is quickly intubated.
- The assistant is instructed not to release pressure on the cricoid cartilage until the cuff of the endotracheal tube is inflated and the position of the tube is confirmed.

Patients undergoing *inhalation induction* progress through three stages: (a) awake, (b) excitement, and (c) surgical level of anesthesia. Adult patients are not good candidates for this type of induction, as the smell of the inhalation agent is unpleasant and the excitement stage can last for several minutes, which may cause hypertension, tachycardia, laryngospasm, vomiting, and aspiration. Children, however, progress through stage 2 quickly and are highly motivated for inhalation induction as an alternative to the IV route. The benefit of postinduction IV cannulation is the avoidance of many presurgical anxieties, and inhalation induction is the most common technique for pediatric surgery.

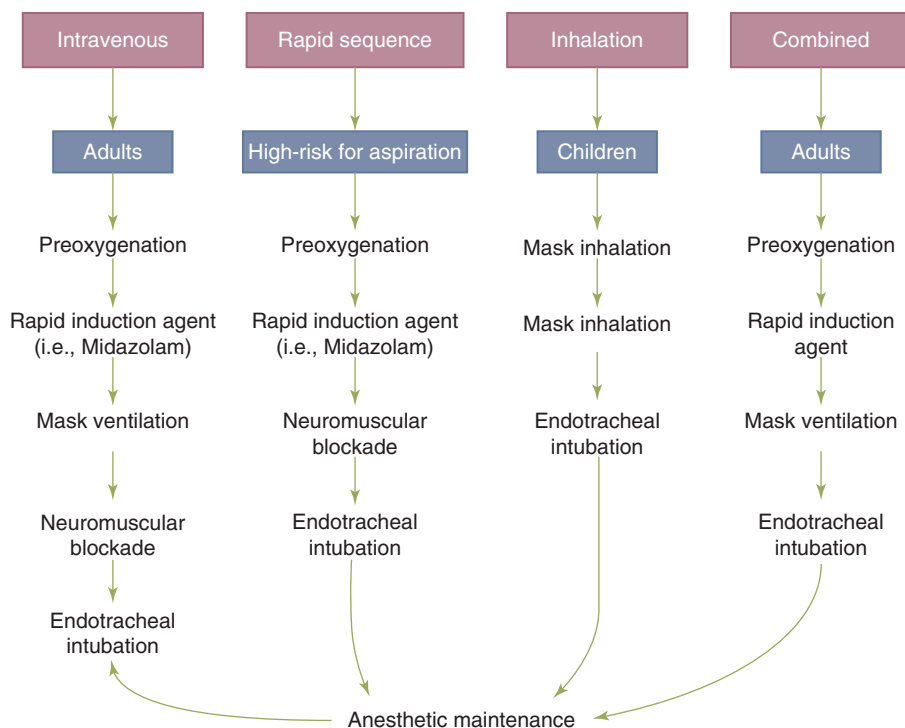


Figure 46-3. Techniques for the induction of general anesthesia.

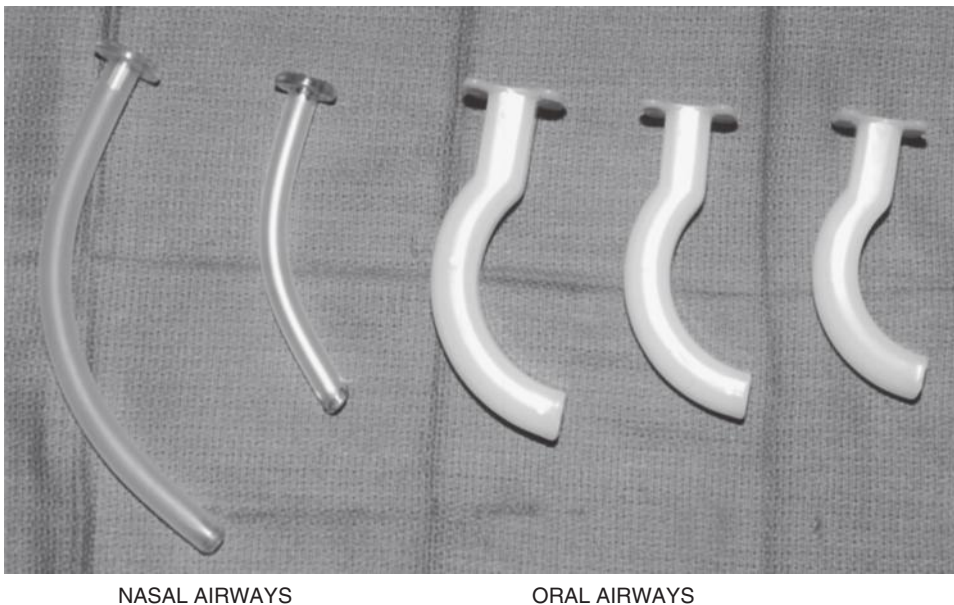


Figure 46-4. From left to right: two nasal airways and three oral airways.

Management of the Airway

After induction of anesthesia, the airway may be managed in several ways, including by face mask, with a laryngeal mask airway (LMA), or, most definitively, by endotracheal intubation with a cuffed endotracheal tube. Nasal and oral airways can help establish a patent airway in a patient being ventilated with a mask by creating an air passage behind the tongue (Fig. 46-4).

The LMA is a cuffed oral airway that sits in the oropharynx. It is passed blindly, and the cuff is inflated to push the soft tissues away from the laryngeal inlet. Because it does not pass through the vocal cords, it does not fully protect against aspiration. It should not be used in patients with a full stomach (Fig. 46-5; lower left). The accurate placement of an endotracheal tube requires skill and proper equipment and conditions. Usually, the patient is unconscious and immobile (including paralysis of the muscles of respiration). Intubation is typically performed under direct visualization by looking through the mouth with a laryngoscope directly at the vocal cords (direct laryngoscopy) and watching the endotracheal tube pass through the cords into the trachea. To obtain a direct line of sight, the patient is placed in the sniffing position. The neck is flexed at the lower cervical spine and extended at the atlanto-occipital joint. This flexion and extension are amplified during laryngoscopy. Laryngoscope handles contain batteries and can be fitted with curved (Macintosh) or straight (Miller) blades (see Fig. 46-5, top row).

Some patients have physical characteristics or a history suggesting difficulty in placing an endotracheal tube. A short neck, limited neck mobility, small interincisor distance, short thyromental distance, and Mallampati class IV may all represent a challenge to endotracheal intubation. Several devices have been developed to assist in management of the difficult airway. The Bullard rigid fiberoptic laryngoscope is a self-contained device that can be passed through a mouth with a narrow opening (Fig. 46-6). The head and neck also can be kept in a neutral position, as a direct line of sight needed with a standard laryngoscope is not necessary. Another new intubating device is the Glidescope, which allows visualization of the vocal cords on a screen (Fig. 46-7)

The intubating laryngeal mask airway (ILMA) is an advanced form of LMA designed to maintain a patent airway as

well as facilitate tracheal intubation with an endotracheal tube. The ILMA can be placed in anticipated or unexpectedly difficult airways as an airway rescue device and as a guide for intubating the trachea. An endotracheal tube can be passed blindly through the ILMA into the larynx, or the ILMA can be used as a conduit for a flexible fiberoptic scope (Fig. 46-8).

The flexible fiberoptic intubation scope is the gold standard for difficult intubation. It is indicated in difficult or compromised airways where neck extension is not desirable or in cases with risk of dental damage. The scope is constructed of fiberoptic bundles and cables encased in a sheath. The cables



Figure 46-5. (Top) Laryngoscopes with curved straight blades. (Bottom) Laryngomask airway, intubating laryngomask airway, and Bullard rigid fiberoptic laryngoscope.



Figure 46-6. The Bullard rigid fiberoptic laryngoscope with endotracheal tube.

permit manipulation of the tip of the scope by adjustments made at the operating end of the device. There is a port for suction and/or insufflation of O_2 . The scope gives excellent visualization of the airway with minimal hemodynamic stress when used properly. It can be used nasally or orally in an awake, spontaneously ventilating patient whose airway has been treated with topical anesthetic. It requires skill for proper use, is expensive, and requires careful maintenance (Fig. 46-9).

The ASA has developed algorithms for management of the difficult airway (Figs. 46-10 and 46-11).⁵¹

Fluid Therapy

Numerous preparations of IV fluid are available for the replacement of perioperative fluid losses in patients undergoing surgery. Different fluid preparations may influence clinical parameters (e.g., platelet function) and may also affect postoperative outcome.



Figure 46-7. Video laryngoscope showing view of vocal cords.

Traditionally, IV fluids have been classified according to whether they are crystalloid or colloid in nature. Crystalloid fluids comprise electrolyte solutions with or without a bicarbonate precursor such as acetate or lactate. The colloids contain a complex sugar or protein suspended in an electrolyte solution. A further distinction between IV fluid types may be based on the nature of the solution. Normal saline-based (0.9% sodium chloride) preparations (crystalloid or colloid) contain no electrolytes other than sodium and chloride. In contrast, balanced salt-based fluids such as lactated Ringer's solution contain other electrolytes, with or without a bicarbonate precursor.

Several types of colloids are available, but three are most commonly used—hydroxyethyl starch (HES), gelatin, and albumin. The HES preparations differ from one another according to their concentration, molecular weight, and extent of hydroxy-ethylation or substitution, with resultant varying physiochemical properties. HES solutions most often are described according to their weight-averaged mean molecular weight in kilodaltons (kDa): high molecular weight (450 kDa), middle molecular weight (200 kDa, 270 kDa), and low molecular weight (130 kDa, 70 kDa). HES 450 kDa solutions are available in a normal saline solution (HES 450/NS) and in a lactated, balanced salt solution (HES 450/BS). Although all of these colloids are used in Europe, gelatins are not available in the United States, and the only HES preparations approved by the U.S. Food and Drug Administration are the 6% high molecular weight (450 kDa) formulations.

The administration of a large volume of any type of IV fluid will cause dilution of platelets and coagulation factors and may lead to coagulopathy (i.e., dilutional coagulopathy). In addition, fluids can have a direct impact on blood clotting through effects on circulating components of the coagulation cascade or by altering platelet function.

Recent evidence suggests that the nature of the solution itself may influence coagulation and bleeding. HES 450/NS may be associated with more bleeding than other fluids. HES 450 in a balanced salt solution appears to be equivalent to 5% albumin

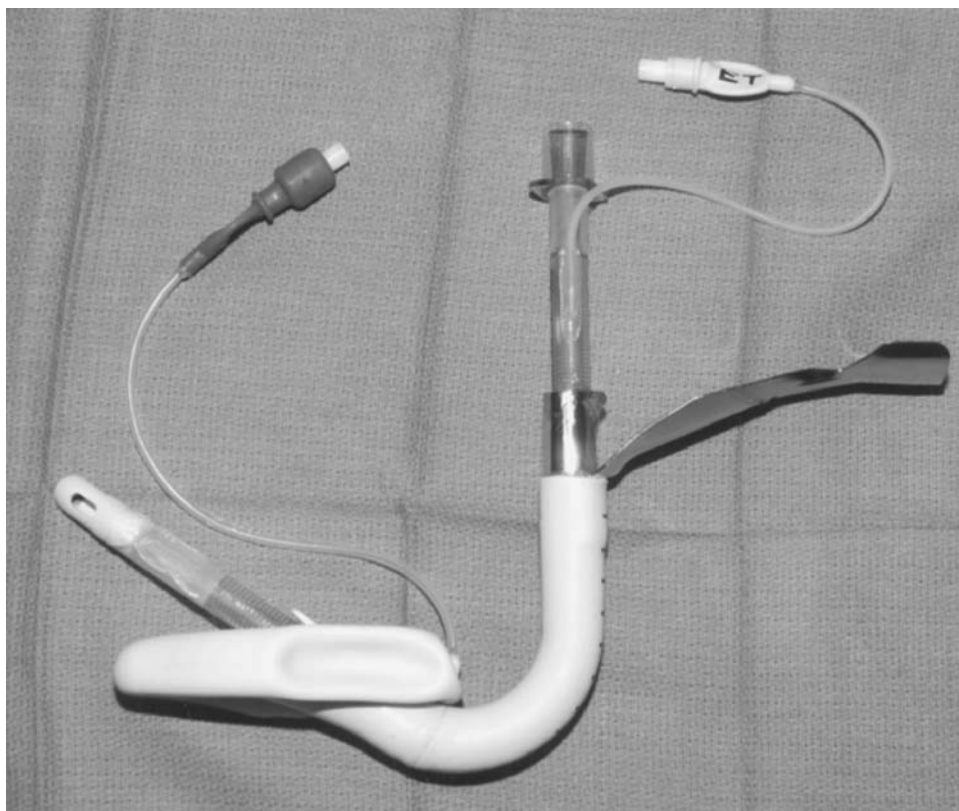


Figure 46-8. Intubating laryngeal mask airway with endotracheal tube.



Figure 46-9. Flexible fiberoptic intubation scope with endotracheal tube.

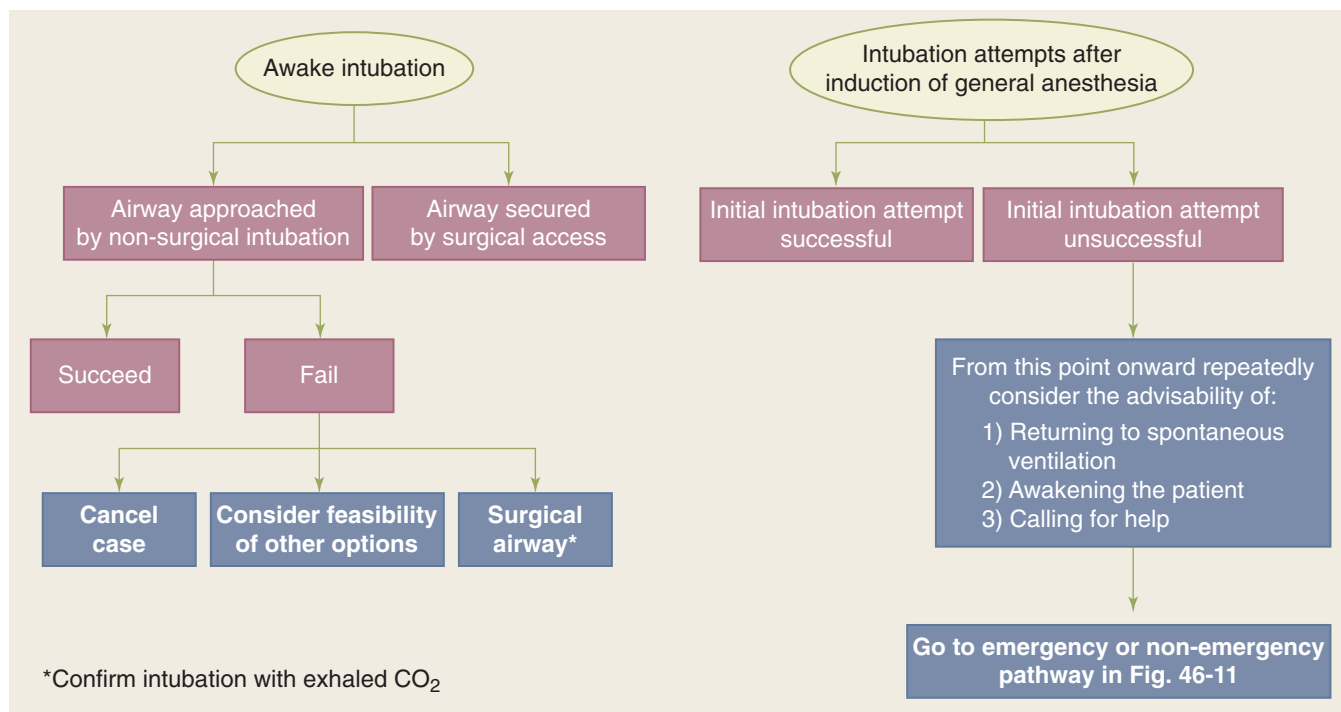


Figure 46-10. American Society of Anesthesiologists airway management algorithm, Part I. CO₂ = carbon dioxide. (Reproduced with permission from *Practice guidelines for management of the difficult airway: An updated report by the American Society of Anesthesiologists Task Force on Management of the Difficult Airway*. Anesthesiology. 2003;98:1269.)

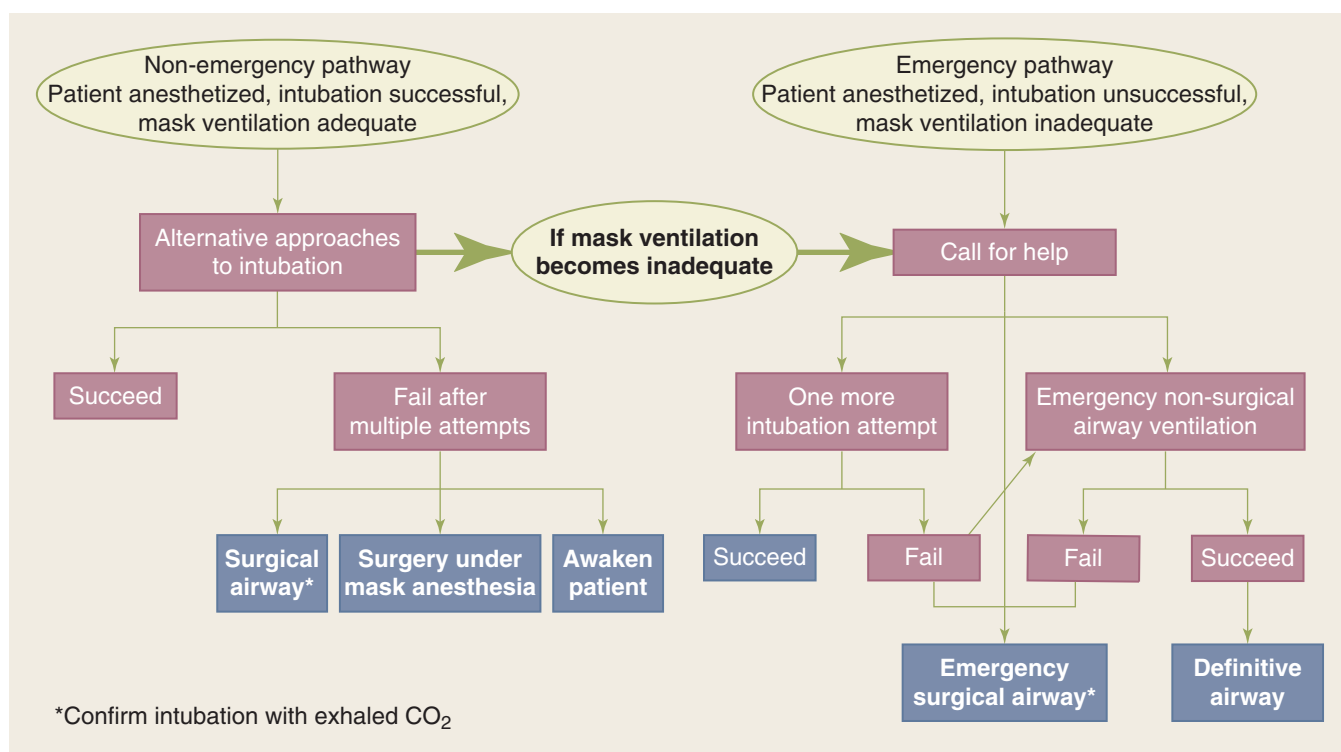


Figure 46-11. American Society of Anesthesiologists airway management algorithm, Part II. CO₂ = carbon dioxide. (Reproduced with permission from *Practice guidelines for management of the difficult airway: An updated report by the American Society of Anesthesiologists Task Force on Management of the Difficult Airway*. Anesthesiology. 2003;98:1269.)

with respect to bleeding outcomes.⁵²⁻⁵⁴ Waters and colleagues reported that patients undergoing abdominal aortic aneurysm repair who received lactated Ringer's solution received smaller volumes of platelets and had less blood product exposure than those treated with normal saline.⁵⁵

It is possible that certain fluids may induce hypercoagulability that may be reflected not only by less bleeding, but also by an increased incidence of postoperative thrombotic complications (e.g., deep vein thrombosis and cerebrovascular accident). There are laboratory data⁵⁶ to suggest that IV fluid administration may induce a hypercoagulable state, but the clinical significance of this remains unclear. The type of fluid administered intraoperatively to a patient can have a significant impact on renal function. The administration of HES/NS or normal saline to critically ill patients or elderly patients undergoing major surgery was associated with the development of renal dysfunction.⁵⁷⁻⁵⁹

The administration of adequate IV fluids during the perioperative period results in a lower incidence of nausea, vomiting, and antiemetic use after minor or day case surgery.⁶⁰ In major noncardiac surgical patients, the administration of HES 450 (in a balanced salt or normal saline solution, or a combination of balanced crystalloid and colloid) has been associated with less postoperative nausea, vomiting, and antiemetic use and earlier return of postoperative bowel function, as reflected by first consumption of solid food, than the administration of 5% albumin, lactated Ringer's solution, or normal saline alone.⁶¹ Studies of patients undergoing ambulatory surgery have shown that perioperative IV fluid administration decreases the incidence of dizziness, drowsiness, thirst, and headache.⁶² In a randomized crossover study of healthy volunteers, subjective deterioration in mental status (lassitude and difficulty in abstract thinking) was reported only by individuals who received 0.9% sodium chloride and not by those who received lactated Ringer's solution.⁶³ The possible effect of different IV fluid preparations on CNS function has not yet been fully explored.

The relative impact of crystalloids and/or colloids on pulmonary function has been the subject of long-standing debate. No difference in postoperative pulmonary function was seen in cardiac surgery patients, orthopedic patients, or urologic surgery patients treated intraoperatively with different colloids.^{57,64,65} In a number of studies in major surgical patients that compared crystalloid (lactated Ringer's solution) with colloid (HES 130/NS, HES 450/NS, 5% albumin/BS),⁶⁶⁻⁶⁸ no difference was seen in the incidence or duration of mechanical ventilation or other indices of respiratory function. These findings suggest that the intraoperative administration of crystalloids does not have a detrimental effect on pulmonary function compared with the administration of colloids.

Transfusion of Red Blood Cells

ABO Blood Groups. There are four different ABO groups, which are determined by whether or not an individual's red blood cells (RBCs) carry the A antigen, the B antigen, both A and B antigens, or neither. From early in childhood, normal healthy individuals make antibodies against A or B antigens that are not expressed on their own cells. People who are group A have anti-B antibodies in their plasma, people who are group B have anti-A antibodies, people who are group O have anti-A and anti-B antibodies, and people who are group AB have neither of these antibodies. These naturally occurring antibodies are mainly immunoglobulin M that attack and rapidly destroy

RBCs. Anti-A antibodies attack RBCs of group A (or AB), and anti-B antibodies attack RBCs of group B (or AB).

ABO-Incompatible Red Cell Transfusion. If RBCs of the wrong group are transfused, in particular if group A RBCs are infused into a recipient who is group O, the recipient's anti-A antibodies bind to the transfused cells. This activates the complement pathways, which damages the red cell membranes and lyses the RBCs. Hemoglobin released from the damaged RBCs is toxic to the kidneys, while the fragments of ruptured cell membranes activate the blood-clotting pathways. The patient suffers acute renal failure and disseminated intravascular coagulation.

Basics of Red Blood Cell Compatibility. Ensuring that the right blood group is transfused is imperative. It is essential to ensure that no ABO-incompatible RBC transfusion is ever given. This avoidable accident is likely to kill or harm the patient. Procedures in which compatibility is determined by establishing both transfusion recipient and donor blood ABO types via crossmatch analysis have evolved over years of clinical and laboratory experience to minimize the risk of this disastrous error. These procedures will continue to evolve as improved computerized systems are introduced to help staff avoid errors in blood administration.

Rhesus D Antigen and Antibody In a white population, about 15% will lack the Rhesus D (Rh D) antigen and are termed Rh D negative. Antibodies to Rh D antigen occur only in individuals who are Rh D negative and as a consequence of transfusion or pregnancy. Even small amounts of Rh D-positive cells entering the circulation of an Rh D-negative person can stimulate the production of antibodies to Rh D, usually immunoglobulin G.

Physiologic Response and Tolerance of Anemia. O₂ is carried in blood in two distinct forms: bound to hemoglobin (Hb) within the RBC and dissolved in the plasma. The actual oxygen content of arterial blood (Cao₂) is determined by the concentration of Hb in the blood, the arterial oxygen saturation of Hb (Sao₂), the O₂-binding capacity of Hb, the Pao₂, and the O₂ solubility of plasma. These variables are interrelated and can be expressed in the following equation:

$$Cao_2 = (Hb \times Sao_2 \times Hb \text{ O}_2 \text{ binding capacity}) + (Pao_2 \times \text{plasma O}_2 \text{ solubility}).$$

Adult Hb consists of four protein chains, each carrying one heme group. One mole of Hb is able to bind to a maximum of 4 moles of O₂. O₂-binding capacity per gram of Hb is 1.39 g/mL. The relationship between Pao₂ and Hb O₂ saturation is shown in Fig. 46-12. The steep part of this curve (partial pressure of oxygen [Po₂] 20–40 mmHg) facilitates O₂ release from Hb. Tissue Po₂ values of different organs are also shown in Fig. 46-12 and lie on this steep part of the curve, facilitating O₂ release from Hb.

Hemodilution and Critical Hematocrit. The intentional dilution of blood volume often is referred to as acute normovolemic hemodilution (ANH) anemia. ANH is a technique in which whole blood is removed from a patient, while the circulating blood volume is maintained with acellular fluid. Blood is collected via central lines with simultaneous infusion of crystalloid or colloid solutions. Collected blood is reinfused after major blood loss has ceased, or sooner, if indicated. Blood units are reinfused in the reverse order of collection. Under conditions of ANH, the increased plasma compartment becomes an important source of O₂, which is delivered to the tissues.

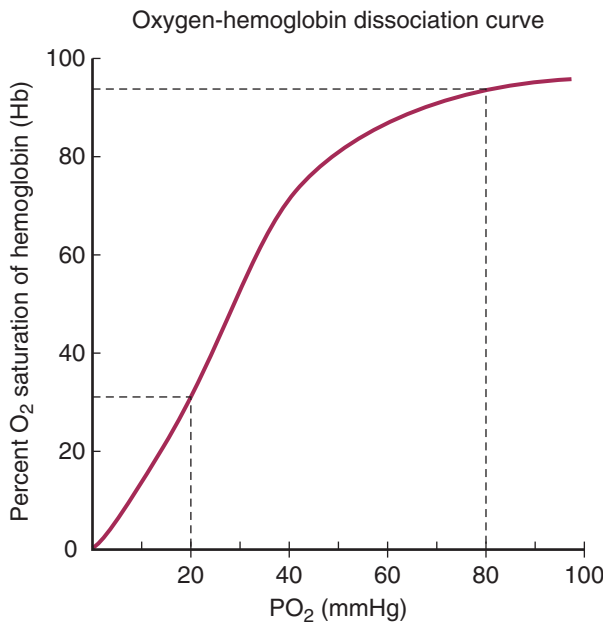


Figure 46-12. Oxygen hemoglobin dissociation curve. O₂ = oxygen; PO₂ = partial pressure of oxygen.

Oxygenation is maintained by increased cardiac output and increased O₂ extraction by the tissues, and when these compensatory mechanisms fail to match the O₂ needs of the tissues, the “critical hematocrit” is said to have been reached. The critical hematocrit has been a source of debate for many years. A theoretical model was developed that describes the relation between hematocrit, myocardial O₂ demand, and the required coronary blood flow during progressive hemodilution.⁶⁹ Using this model, the determinants of critical hematocrit and the limits of ANH can be calculated based on the limits of coronary reserve. Because the critical hematocrit varies with O₂ consumption and degree of CAD, a fixed critical hematocrit as a transfusion trigger is not appropriate in most patients. Rather, the indication for blood transfusions must individually take into account the specific circumstances of the patient, such as expected blood loss and required O₂ transport capacity reserves, hemodynamic stability, CAD, and systemic O₂ consumption.

RECOVERY FROM ANESTHESIA

Reversal of Neuromuscular Blockade

The elimination of neuromuscular blocking agents from the body and subsequent resumption of neuromuscular transmission takes a considerable amount of time, even with drugs such as vecuronium that have relatively short half-lives. Additionally, it is time consuming to wait for complete spontaneous recovery at the end of a surgical procedure. Therefore, it has become routine to antagonize the neuromuscular block pharmacologically with the use of reversal agents. Reversal agents raise the concentration of the neurotransmitter acetylcholine to a higher level than that of the neuromuscular blocking agent. This is accomplished by the use of anticholinesterase agents, which reduce the breakdown of acetylcholine. The most commonly used agents are neostigmine, pyridostigmine, and edrophonium.

The common side effects of these three anticholinesterase agents are bradycardia, bronchial and intestinal smooth muscle contractions, and excessive secretions from salivary and bronchial glands. These effects are primarily mediated by effects on muscarinic receptors, which are effectively blocked by the concomitant use of antimuscarinic drugs such as atropine or glycopyrrolate. To ensure adequate ventilation postoperatively, it is important that the neuromuscular blocking agents are fully reversed, as assessed by monitoring twitch strength with a nerve stimulator and clinically correlating this with signs such as grip strength or 5-second head lift.

The Postanesthesia Care Unit

It is of primary importance that all patients awakening from anesthesia are followed in a recovery room, as approximately 10% of all anesthetic accidents occur in the recovery period. As more serious surgeries are performed on older and sicker patients, the number of patients requiring postoperative ventilation and medications to support their circulation increases with age. The new trend for postoperative pain control with continuous epidural administration of local anesthetics and narcotics demands close observation, because respiratory depression can occur. In most hospitals, the number of intensive care beds is too small to accommodate the increasing number of these patients. What originally began as the recovery room now must function as an intensive care unit setting for short stays. The name “recovery room” has been changed to postanesthetic care unit (PACU). A variety of physiologic disorders that can affect different organ systems need to be diagnosed and treated in the PACU during emergence from anesthesia and surgery. Postoperative nausea and vomiting (PONV), airway support, and hypotension requiring pharmacologic support have been observed to be the most frequent complications in the PACU.⁷⁰ Abnormal bleeding, hypertension, dysrhythmia, myocardial infarction, and altered mental status are not uncommon.⁷⁰

Postoperative Nausea and Vomiting

PONV typically occurs in 20% to 30% of surgical cases,⁷¹ with considerable variation in frequency reported between studies (range, 8%–92%).⁷² PONV is generally considered a transient, unpleasant event carrying little long-term morbidity; however, aspiration of emesis, gastric bleeding, and wound hematomas may occur with protracted or vigorous retching or vomiting. Troublesome PONV can prolong recovery room stay and hospitalization and is one of the most common causes of hospital admission following ambulatory surgery. Published evidence suggests that prophylactic administration of antiemetics is not cost-effective in the surgical setting.⁷³ Recent consensus guidelines using data from systematic reviews, randomized trials and studies, and logistic regression models have been published (Fig. 46-13).⁷³

Agents usually administered for PONV are the serotonin receptor antagonists (e.g., ondansetron, dolasetron, granisetron, and tropisetron). The safety and efficacy of the compounds, when given at the end of surgery, are virtually identical.^{73,74} Metoclopramide (not a true antiemetic), when used in the standard dose of 10 mg, is ineffective for PONV.⁷⁵ Although some studies have shown higher doses (20 mg) to have some effect on PONV, most evidence suggests that the serotonin receptor antagonists are the most efficacious choice.

Pain: The Fifth Vital Sign

Analgesic research methodology has been enhanced since the 1960s through the use of graduated and visual analog scales,

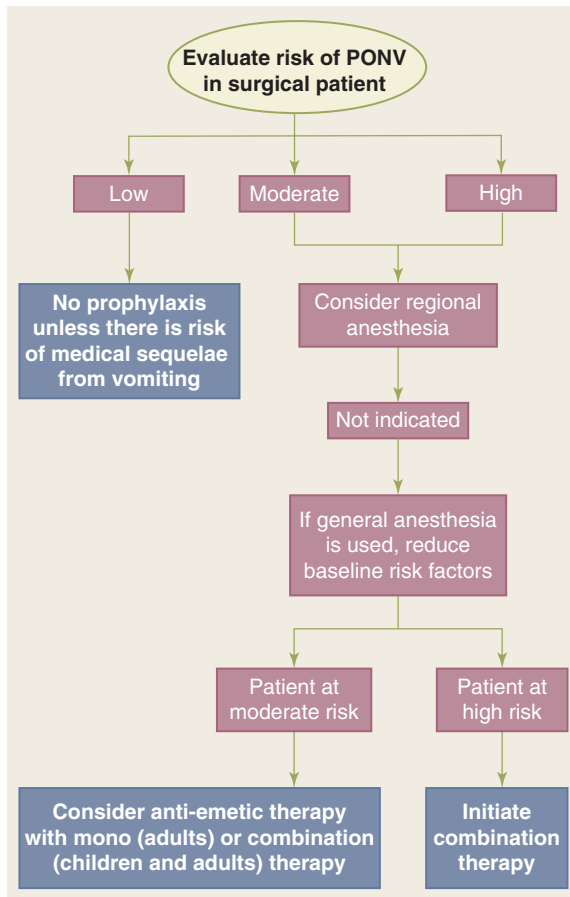


Figure 46-13. Algorithm for the management of postoperative nausea and vomiting (PONV). (Reproduced with permission from Gan TJ, Meyer T, Apfel CC, et al: *Consensus guidelines for managing postoperative nausea and vomiting*. *Anesth Analg*. 2003;97:62.)

tools that permit the standardization of pain scores. One frequently used graduated scale is a four-point measure of pain intensity (0 = no pain, 1 = mild pain, 2 = moderate pain, and 3 = severe pain) and a five-point measure of relief (0 = no relief, 1 = a little relief, 2 = some relief, 3 = a lot of relief, and 4 = complete relief).

Acute postoperative pain and its treatment (or prophylaxis) are significant challenges for the healthcare professional. Despite the recent development of new nonnarcotic analgesics and a better understanding of the side effects associated with pain medication of all types, acute postoperative pain remains a significant concern for patients and represents an extremely negative experience for patients undergoing surgery. Many patients experience pain in the postoperative period despite the use of potent techniques such as patient-controlled analgesia, epidural analgesia, and regional anesthesia. The culture of acceptance of postoperative pain is changing. The American Pain Society has advocated the assessment of pain as the fifth vital sign, along with temperature, pulse, blood pressure, and respiratory rate. The four vital signs provide a quick snapshot of a patient's general condition, but pain management advocates claim the picture is not complete without including pain as the fifth vital sign.

This approach may improve the efficacy of pain treatment. Many departments of anesthesiology support an active pain



Figure 46-14. Use of ultrasound to identify the popliteal nerve for analgesia of the ankle.

service and provide consultation for postoperative pain relief, including the administration of nerve blocks.

MULTIMODAL ANALGESIA

Opioids, long the staple of postoperative pain management, reduce pain by acting on the μ -receptor. Analgesia is accompanied by unwanted side effects also promulgated by the μ -receptor (e.g., sedation, nausea and vomiting, constipation, respiratory depression). Reducing opioid use and those side effects by the addition of nonopioid analgesics is called multimodal analgesia.⁷⁶ Analine derivatives (IV acetaminophen),⁷⁷ NSAIDs like celecoxib⁷⁸ and ketorolac,⁷⁹ steroids (dexamethasone),⁸⁰ and anticonvulsants (gabapentin and pregabalin)^{81,82} have all been used as opioid-sparing methods to attenuate postoperative pain. The best mixture of drugs is yet to be found; continued work is necessary to find the idea combination.⁸³

Regional analgesia, (i.e., nerve blocks) is an effective method for reducing postoperative pain while minimizing opioid consumption. Nerve blocks can be of the upper or lower extremities, truncal, epidural, or paravertebral (Fig. 46-14).

THE TRANSVERSUS ABDOMINIS PLANE BLOCK

The transversus abdominal plane (TAP) block is truncal regional analgesia that results in analgesia to the anterior abdominal wall and has rapidly gained popularity. Pain secondary to any transgression of the abdominal wall can be attenuated by a TAP block, including laparoscopic procedures⁸⁴; vertical or Pfannenstiel incisions; inguinal,⁸⁵ incisional, or umbilical hernia repair; hysterectomy; cholecystectomy; and appendectomy (Figs. 46-15–46-18).⁸⁶⁻⁸⁸

Somatic nerves supplying the abdominal wall travel in the plane between the internal oblique muscle and the transversus abdominis muscle (Fig. 46-19). Injection of local anesthetic into this plane under ultrasound guidance results in pain relief for 8 to 12 hours (Figs. 46-20–46-22).



Figure 46-15. Kidney transplant recipient incisions.



Figure 46-17. Laparoscopy incisions.



Figure 46-16. Inguinal hernia incisions.



Figure 46-18. Pain from these incisions is reduced by transversus abdominal plane block.

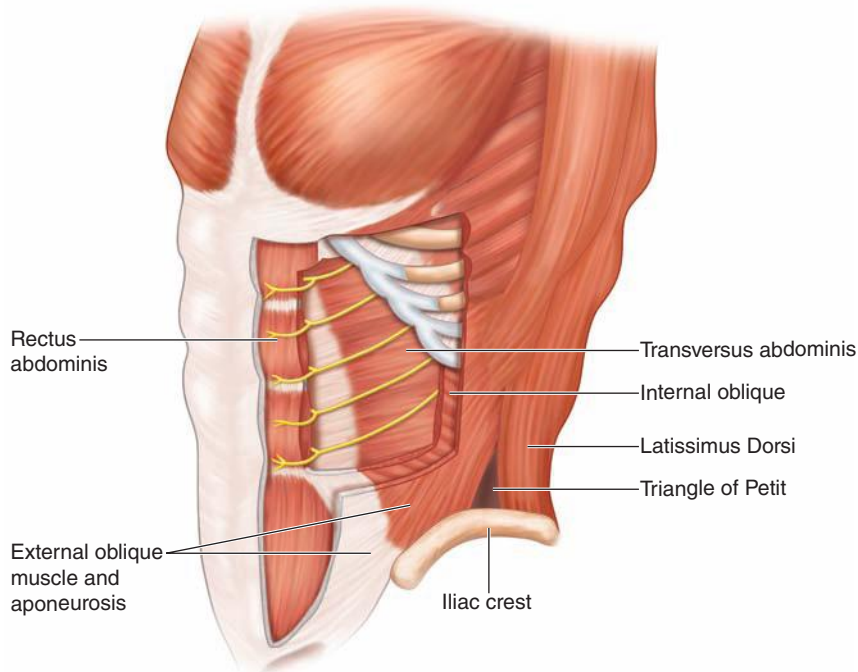


Figure 46-19. Sensory nerves travel to the anterior abdominal wall in the plane between the internal oblique and transversus abdominis muscles. (Reproduced with permission from *Ultrasound for Regional Anesthesia* website, www.usra.ca.)



Figure 46-20. The use of ultrasound to perform a transversus abdominal plane block.

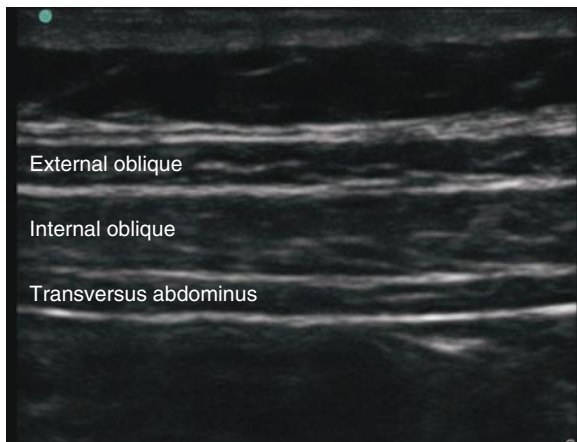


Figure 46-21. Ultrasound view of external oblique, internal oblique, and transversus abdominis muscles.

MALIGNANT HYPERTHERMIA

Malignant hyperthermia (MH) is a hereditary, life-threatening, hypermetabolic acute disorder, developing during or after receiving general anesthesia.⁸⁹ The clinical incidence of MH is about 1:12,000 in children and 1:40,000 in adults. A genetic predisposition and one or more triggering agents are necessary to evoke MH. Triggering agents include all volatile anesthetics (e.g., halothane, enflurane, isoflurane, sevoflurane, and desflurane) and the depolarizing muscle relaxant succinylcholine. Volatile anesthetics and/or succinylcholine cause a rise in the myoplasmic calcium concentration in susceptible patients, resulting in persistent muscle contraction.

MH is an autosomal dominant disorder associated with several gene loci, predominantly the ryanodine receptor gene *RYR1*. MH can be diagnosed with the caffeine-contraction halothane test (which requires muscle biopsy). Genetic testing is helpful after the fact; there is no simple reliable blood screening test yet available.

The classic MH crisis entails a hypermetabolic state, tachycardia, and the elevation of end-tidal CO_2 in the face of constant minute ventilation. Respiratory and metabolic acidosis and muscle rigidity follow, as well as rhabdomyolysis,

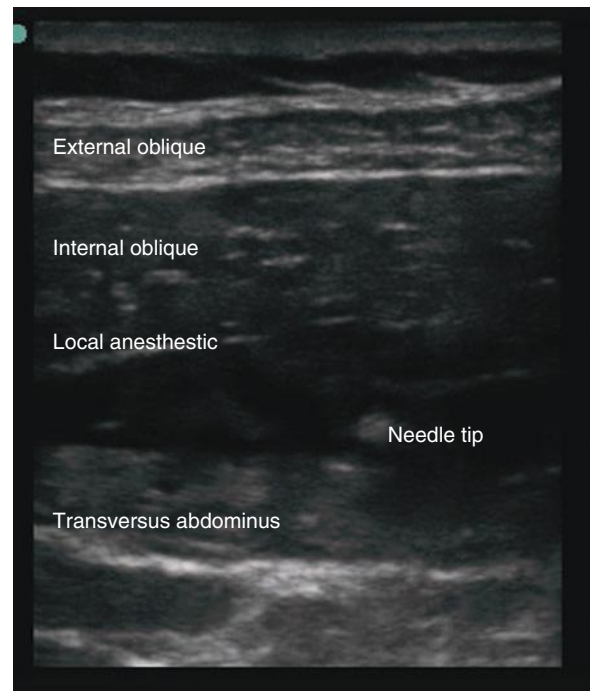


Figure 46-22. Ultrasound image of local anesthetic above the transversus abdominis.

arrhythmias, hyperkalemia, and sudden cardiac arrest. A rise in temperature is often a late sign of MH. Treatment must be aggressive and begin as soon as a case of MH is suspected:

- Call for help.
- Stop all volatile anesthetics and give 100% O_2 .
- Hyperventilate the patient up to three times the calculated minute volume.
- Give bicarbonate to treat acidosis if dantrolene is ineffective.
- Treat hyperkalemia with insulin, glucose, and calcium.
- Avoid calcium channel blockers
- Begin infusion of dantrolene sodium, 2.5 mg/kg IV. Repeat as necessary, titrating to clinical signs of MH. Repeat dantrolene at 1 mg/kg every 6 to 8 hours at least twice, and monitor the patient in an intensive care unit setting for 24 hours or more for possible recrudescence.
- Call the MH hotline to report the case and get advice: 1-888-274-7899.

FUTURE DIRECTION OF ANESTHESIA

The general mantra of “gene therapy is the future of medicine” must be more specifically related to how those genes create, shape, and regulate proteins. The study of how proteins manifest their activity and/or concentration is called proteomics (from proteome—a fusion of “protein” and “genome”).

As the technology advances to biologically identify individual proteins, studies of individual levels of proteomes will allow the study of disease processes on the molecular level, directly aiding diagnosis and therapeutics.⁹⁰

Specifically to the field of anesthesiology, the technology of proteomics will be used to elucidate the actual mechanism of action of our anesthetic drugs and how these drugs have differing effects on different individuals. There will be a day when a

buccal swab in the preoperative clinic will become routine, with the results telling us which opioids carry the fewest side effects for that particular patient, for example, or which antiemetics are most effective, or which postoperative analgesics to use—a tailored anesthetic.

Recent studies in mice have examined the $\alpha 5$ subunit of the GABA receptor, which appears to regulate memory. The human genome is polymorphic for the $\alpha 5$ gene; because each variant may manifest in different amounts of memory/amnesia, proteomics may someday lead to tests that determine the propensity of a particular patient to experience awareness and allow us to tailor the anesthetic even further.⁹¹

Genetic testing for cytochrome P450 deficiencies is now commercially available.⁹² As the number of enzymes able to be tested increases, we will be able to choose the most appropriate match between drug and patient.

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47 chapter

Surgical Considerations in the Elderly

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GENERAL CONSIDERATIONS

As our population ages, a dramatic increase is anticipated in the number of geriatric patients that will require various surgical interventions. The U.S. Census Bureau estimates that the number of people age 65 years and older will double between 2010 and 2050.¹ By 2030, people 65 years of age or older will account for 20% of the overall population. Furthermore, half of all Americans currently alive can expect to reach the ninth decade of life.² Geriatric patients represent a unique surgical challenge due to the complexity of comorbid conditions coupled with the physiologic changes that occur with aging. As a result of these considerations, and in response to research and specialized care protocols which are tailored for its age range, geriatric surgery has emerged as a subspecialty of surgery much as pediatric surgery developed decades ago.

Physiologic age is of greater importance in perioperative management of elderly surgical patients than chronologic age because it takes into account the burden of comorbid disease. It is, therefore, an accurate predictor of postoperative morbidity and mortality. The hallmark of physiologic aging or “senescence” is decreased functional reserve of critical organ systems, resulting in the decreased ability of these systems to respond to a challenge, with surgical stress being a prime example. The age of 70 years is typically accepted as the start of senescence because age-related organ dysfunction and the development of comorbid conditions sharply increases between ages 70 and 75 years.³ This criterion for senescence is in contrast to clinical studies published just 50 years ago that categorized elderly patients as those over the age of 55 years. With improved technologies and expanded criteria for surgical interventions in extremely aged patients, increased awareness of the special needs of this population is required to ensure a comprehensive preoperative assessment, delivery of optimal surgical care, and minimization of postoperative complications. It is also critical that a multidisciplinary approach be developed, which involves the patient and their home caregivers, geriatric physicians, surgeons, and, at times, specialists in intensive care.

It is estimated that, by the year 2030, there will be 70 million people >65 years old in the United States, a stark increase over the 35 million in 2000.⁴ This ever growing elderly population will increasingly require surgical care, and patients >65 years old already account for approximately 60% of the general surgeon’s workload.⁵ Patients >65 years old account for approximately 50% of all emergent operations and 75% of operative mortality.⁴ These statistics challenge a surgeon to have an in-depth understanding of the careful perioperative evaluation required in elderly patients and the tailoring of surgical interventions based on the unique changes in physiologic reserve and comorbid conditions that make elderly patients more susceptible to postoperative complications.

The goal of this chapter is to highlight salient management strategies for aged surgical patients to achieve optimal care and reduce postoperative complications. Particular problems in the elderly population which impact on surgical care include the potential delay in surgical treatment due to a missed or delayed diagnosis secondary to an atypical presentation of disease, and the postponement of needed elective surgery because of the misconception that an elderly patient will suffer a poor outcome as a result of advanced age alone. For example, elective inguinal and umbilical hernia repairs are often postponed due to age bias; this can lead to potentially devastating consequences of bowel ischemia, gangrene, and perforation, to which elderly patients respond poorly. As a result, emergency hernia repairs are among the most common procedures performed in older patients; approximately 40% of hernia repairs are performed for incarceration or bowel obstruction in patients >65 years old.⁵ Emergency repair of hernias is associated with an increased morbidity rate of approximately 50% and a mortality rate ranging between 8% to 14%; a significant increase from the 2% mortality rate following elective repair in age-matched patients.⁵

Another significant consideration with the geriatric population is the need to balance optimal health care delivery with rising health care costs. The goal of surgical therapy in the elderly is to provide needed interventions which result in maximum benefit to the patient without compromising quality of life or

Key Points

- 1▶ Frailty, dementia, and geriatric syndromes have recently been identified as major factors in the development of postoperative complications in the elderly.
- 2▶ Emergency surgery in the elderly carries a mortality rate that is 3 to 4 times that seen after elective surgery.
- 3▶ Impaired cardiac function is responsible for more than half of the postoperative deaths in elderly patients, so careful attention must be paid to intravascular volume status in the perioperative period.
- 4▶ In elderly patients with acute appendicitis or acute cholecystitis, one-third lack fever, one-third lack an elevated white blood cell count, and one-third lack physical findings of peritonitis.
- 5▶ Physiologic age, not chronologic age, is the consequence of diminished functional reserve due to comorbid conditions, and is the major predictor of perioperative morbidity and mortality in the elderly.
- 6▶ Laparoscopic approaches to surgical management, including the use of exploratory laparoscopy to rule out surgical disease, are associated with fewer complications and more rapid recovery in the elderly.
- 7▶ New tools exist to help assess perioperative risk in geriatric patients, in addition to medical comorbidities. They include identification of geriatric syndromes, frailty indicators.

unwanted adverse outcomes. For example, screening for breast or colorectal cancer should be performed if the patient has a reasonable expectation of quality and quantity of life. An extensive and/or invasive workup should not be performed if the patient would not tolerate the anticipated therapeutic intervention.

Finally, a fifth of elderly patients die in ICU settings and half of them require mechanical ventilation and a quarter undergo cardiopulmonary resuscitation in the days before their death.⁶ Although Medicare expenditures in the last year of life are approximately five times higher than in nonterminal years, the actual quality of care at the end of life is often poor due to debilitating and persistent symptoms. Even more worrisome is the fact that some patients receive treatments which are inconsistent with their preferences for end of life measures. An additional component of geriatric surgery is therefore the provision of compassionate care that is more focused on symptomatic relief than on cure in patients who are near the end of life.

PHYSIOLOGY OF AGING

Elderly surgical patients are a heterogeneous cohort with various degrees of functional impairments and comorbid burdens. The “young old patient” may lead an active lifestyle with few, if any, comorbid conditions. But even for this seemingly healthy individual, it is crucial to remember that there are inherent physiologic changes that occur with aging and which affect every organ system. These physiologic changes may become more apparent and clinically consequential with the stress of major illness and operative interventions.

An important criterion in the geriatric surgery patient is the frailty score. Frailty is a syndrome associated with advanced age that results from decreased physiologic reserve and which makes patients less resistant to major stressors such as invasive surgical procedures. Frail patients are prone to poorer outcomes, due to falls, disability, impaired ability to perform activities of daily living (ADLs), prolonged hospitalizations and an increase in mortality.¹ Frail patients are more likely to require discharge to skilled nursing facilities postoperatively. Prior to surgery, frail patients and their family members should be aware of this possibility. Therefore, the frailty score is a more accurate representation of the patient’s physiologic age.

Chronologic age is rarely an accurate predictor of morbidity and mortality from surgical interventions. It is, however,

an accurate marker for declining physiologic reserve and the likelihood of the presence of comorbid conditions. These place elderly patients at higher risk because of impaired cardiac, pulmonary, renal, and neurological reserves, which increase the morbidity and mortality risk of surgical interventions. Physiologic age, in addition to comorbid conditions, more accurately predicts surgical outcomes in the elderly than chronologic age. The physiologic changes of aging are summarized in Table 47-1.

The terms “frailty,” “disability” and “comorbidity” have mistakenly been used interchangeably. These terms have very different connotations for the geriatric patient. Disability is defined as dependence on assistance with ADLs, and contributes to the risk of frailty. Comorbidity is defined as the presence of two or more existing diseases, and is quantified by the Charlson comorbidity index.⁷ Geriatric assessment markers for frailty and disability include cognition, albumin level, history of falls, hematocrit level, and dependence on assistance with ADLs. These objective measures have been shown to predict six month postoperative mortality or the need for long term institutionalized care after surgery.⁷ (Table 47-2)

SURGERY IN THE ELDERLY

It is critical in the assessment of any elderly patient to maintain a high index of suspicion for surgical pathology. Elderly patients often present with atypical symptoms and/or a misleadingly benign-appearing abdominal examination that may mask an intra-abdominal catastrophe. The effects of age-related impairments in immune function can be compounded by co-existent medical problems and altered mentation as a result of dementia, drugs, infection, or dehydration.

Acute appendicitis and acute cholecystitis are classic examples of common acute surgical pathologies in which elderly patients have a delay in diagnosis or misdiagnosis. This often leads to higher rates of perforation and complications that adversely affect morbidity and mortality.⁸ Biliary tract disease, including acute cholecystitis, is the most common indication for surgical intervention in the elderly. This is likely related to age-related changes within the biliary system, such as increased lithogenicity of bile and an increased prevalence of cholelithiasis. Delayed diagnosis due to atypical or misleading symptoms may lead to complications such as ascending cholangitis, gallbladder perforation, or gallstone ileus.

Table 47-1

Physiologic limitations of aging, their clinical consequences, and “best practices” in the elderly surgical patient.

AGE-RELATED CHANGES	CLINICAL CONSEQUENCES	BEST PRACTICES
Body Composition		
<ul style="list-style-type: none"> Significantly decreased muscle mass, accounting for much of decreased lean tissue mass Increased fat mass 	<ul style="list-style-type: none"> Erosion of muscle mass during acute illness may result in strength rapidly falling below important clinical thresholds (e.g., impaired coughing, decreased mobility, increased risk of venous thrombosis) Altered volumes of drug distribution 	<ul style="list-style-type: none"> Maintain physical function through effective pain relief, avoiding tubes, drains, and other “restraints,” early mobilization, and assistance with mobilization. Minimize fasting, provide early nutritional supplementation or support (both protein-calorie and micronutrient). Adjust drug dosages for volume of distribution.
Respiratory		
<ul style="list-style-type: none"> Decreased vital capacity Increased closing volume Decreased airway sensitivity and clearance Decreased partial pressure of oxygen 	<ul style="list-style-type: none"> Less effective cough Predisposition to aspiration Increased closure of small airways during tidal respiration, especially postoperatively and when supine, leading to increased atelectasis and shunting Predisposition to hypoxemia 	<ul style="list-style-type: none"> Provide early mobilization, assumption of upright rather than supine position. Ensure effective pain relief to allow mobilization, deep breathing. Provide routine supplemental oxygen in the immediate postoperative period, and then, as needed. Minimize use of nasogastric tubes.
Cardiovascular		
<ul style="list-style-type: none"> Decreased maximal heart rate, cardiac output, ejection fraction Reliance on increased end-diastolic volume to increase cardiac output Slowed ventricular filling, increased reliance on atrial contribution Decreased baroreceptor sensitivity Thermoregulation Diminished sensitivity to ambient temperature and less efficient mechanisms of heat conservation, production, and dissipation Febrile responses to infection may be blunted in frail or malnourished elderly and those at extreme old age. 	<ul style="list-style-type: none"> Greater reliance on ventricular filling and increases in stroke volume (rather than ejection fraction) to achieve increases in cardiac output Intolerant of hypovolemia Intolerant of tachycardia, dysrhythmias, including atrial fibrillation Predisposition to hypothermia (e.g., decline in body temperature during surgery is more marked unless preventive measures are taken) If there is hypothermia, shivering may result, associated with marked increases in oxygen consumption and cardiopulmonary demands. Fever may be absent despite serious infection, especially in frail elderly. 	<ul style="list-style-type: none"> Use vigorous fluid resuscitation to achieve optimal ventricular filling. Nonvasoconstricting inotropes and afterload reduction may be more effective, if pharmacologic support is required. Use active measures to maintain normothermia during surgical procedures and to rewarm after trauma: warmed IV fluids, humidified gases, warm air. Maintaining intraoperative normothermia reduces wound infections, adverse cardiac events, and length of hospital stay. Be aware of hypothermia in trauma resuscitation.

(Continued)

Table 47-1

Physiologic limitations of aging, their clinical consequences, and “best practices” in the elderly surgical patient. (continued)

Renal function, fluid-electrolyte homeostasis

<ul style="list-style-type: none">• Decreased sensitivity to fluid, electrolyte perturbations• Decreased efficiency of solute, water conservation, and excretion• Decreased renal mass, renal blood flow, and glomerular filtration rate• Increased renal glucose threshold	<ul style="list-style-type: none">• Predisposition to hypovolemia• Predisposition to electrolyte disorders, (e.g., hyponatremia)• Predisposition to hyperglycemia• Predisposition to hyperosmolar states	<ul style="list-style-type: none">• Pay meticulous attention to fluid and electrolyte management.• Recognize that a “normal” serum creatinine value reflects decreased creatinine clearance because muscle mass (i.e., creatinine production) is decreased concurrently.• Select drugs carefully: Avoid those that may be nephrotoxic (e.g., aminoglycosides) or adversely affect renal blood flow (e.g., NSAIDs).• Adjust drug dosages as appropriate for altered pharmacokinetics.
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Source: Reproduced with permission from Watters JM: Surgery in the elderly. *Can J Surg* 45:106, 2002. © 2002 Canadian Medical Association.

Elderly patients with acute peritonitis may not present with typical symptoms of acute abdominal pain, fever, or leukocytosis, due to a depressed immune response. In older patients presenting with acute appendicitis, the initial diagnosis is correct in less than half of the patients.⁸ A careful assessment and high index of suspicion are crucial to achieve timely operative intervention.

PREOPERATIVE ASSESSMENT

Surgical risk increases with advancing age as a consequence of physiologic decline and the development of comorbid conditions that make the elderly surgical patient more susceptible to postoperative complications. Geriatric patients may have masked vulnerabilities due to their unique physiologic state that requires a more detailed preoperative assessment. Comorbid illness serves as the basis for the American Society of Anesthesiologists’ (ASA) physical status classification. This is a valuable tool for identifying elderly patients who are at high risk for postoperative complications because it is based on organ system dysfunction and severity of functional impairment. It helps to identify subgroups of patients in whom appropriate measures should be taken to reduce the risk of adverse outcomes.

Table 47-2

Frailty, disability, and comorbidities measures which are significant preoperative predictors of outcomes in the geriatric patient.⁷

MARKER	MEASURE
Frailty	Cognition (Mini-Cog test ≤ 3) Falls ≥ 1 in last six months Albumin ≤ 3.3 gm/dL Hematocrit $\leq 35\%$
Disability	DependenceDependence on ≥ 1 activity of daily living
Comorbidity	Charlson index ≥ 3

2▶ Importantly, it also quantifies the risks of morbidity and mortality for emergency surgery. A careful assessment of potential problems in the perioperative period combined with implementation of preventative measures can significantly reduce complications associated with general anesthesia in the elderly patient.⁹ A useful algorithm for the preoperative assessment of an elderly surgical patient is provided in Fig. 47-1.

Cardiac complications are the leading cause of perioperative complications and death in surgical patients of all age groups, but particularly among the elderly. This is because patients often have co-existing cardiac dysfunction, combined with normal physiologic decline and poor functional reserve. The combined effect of depletion of intravascular volume, age-related impairment of response to catecholamines, and increased myocardial relaxation time adversely affects the cardiac function of an elderly patient under stress in the perioperative period.¹⁰ Aging has been demonstrated to cause a decrease in cardiac output by approximately 1% per year. Older individuals fail to augment heart rate to the same extent as younger individuals. More importantly, the ability to increase cardiac output with aging is dependent on ventricular dilatation, which is determined by preload.¹¹ Therefore careful attention must be paid to volume status in the perioperative period. Dehydration or poor resuscitation may occur in elderly surgical patients for a variety of reasons, and both are poorly tolerated. Over one half of all postoperative deaths in elderly patients and 11% of postoperative complications are a result of impaired cardiac

3▶ function under physiologic stress. Incomplete emptying of the ventricle at end systole and subsequent reduction in ejection fraction is characteristic of the aging heart.¹⁰ Reduced distensibility, in addition to acute stressors, leads to impaired coronary perfusion and cardiac ischemia.

As a result, the physiologic stress of general anesthesia and surgical interventions can unmask the limited cardiac reserve of the elderly patient. Poor reserve may become evident with increased myocardial oxygen demand resulting from tachycardia or loss of vascular tone from the vasodilatory effects of many general anesthetic agents. An important predictor of surgical

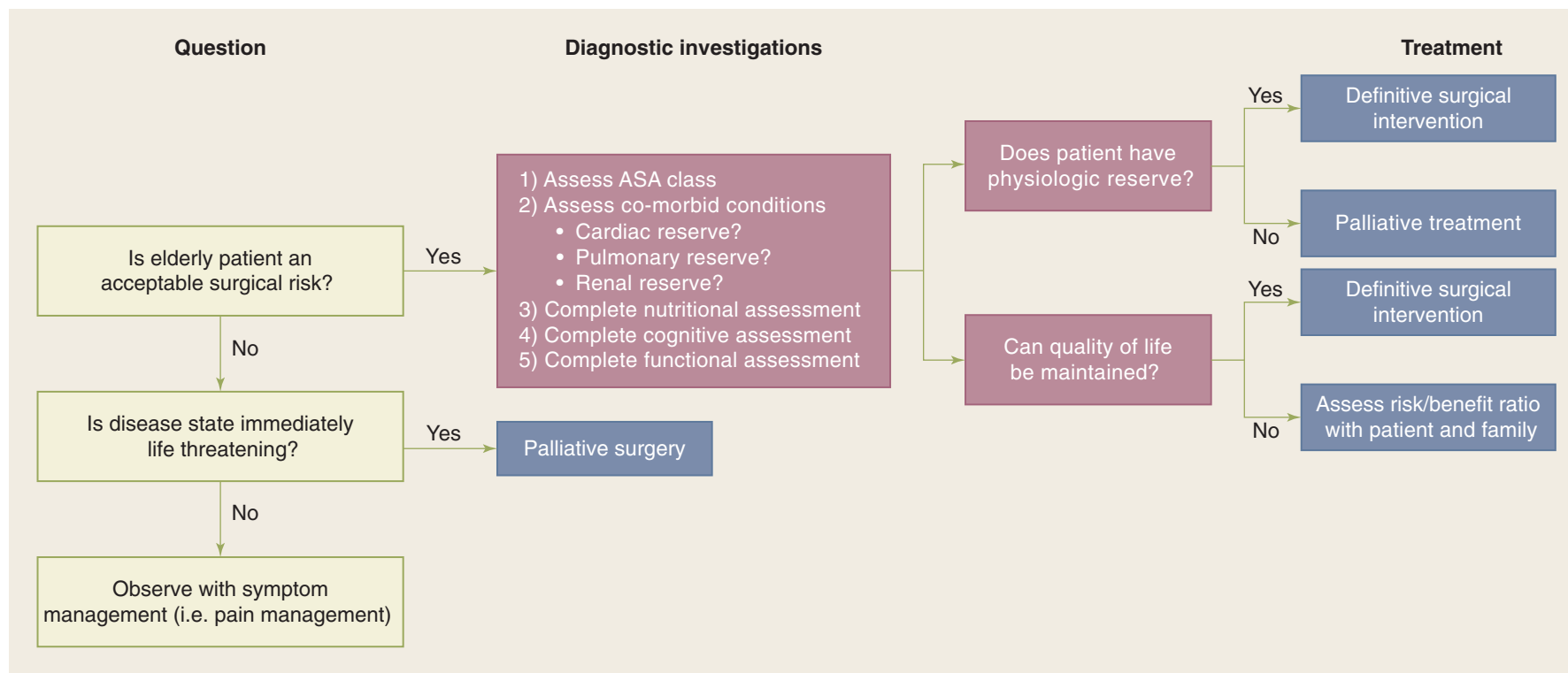


Figure 47-1. Useful preoperative algorithm to determine elderly patient's suitability for definitive surgical intervention balancing therapeutic goals, physiologic reserve, and quality of life with palliative treatment and surgery as viable options. ASA = American Society of Anesthesiologists.

outcomes and cardiac complications in the elderly is congestive heart failure (CHF). CHF is present in approximately 10% of patients older than 65 years and is the leading cause of postoperative morbidity and mortality.¹² This prevalence will likely increase as percutaneous interventions and medical therapy prolongs survival from myocardial ischemia and acute myocardial infarction. Therefore, identifying correctable and uncorrectable cardiovascular disease is critical before elective surgical interventions.

Pulmonary complications are a major source of morbidity and mortality in elderly surgical patients. The age-related changes that occur in the respiratory system limits the maximal breathing capacity by age 70 to 50% of the capacity present at age 30.¹² In addition, there is a decline in the forced expiratory volume in 1 second (FEV1) with advancing age. It is estimated that humans lose 35 mL of their FEV1 per year over the age of 35 years old. There is a slow decline between ages 35 and 65 years old followed by a much more progressive decline at approximately 75 years of age.¹³ Pulmonary complications account for up to 50% of postoperative complications and 20% of preventable deaths.¹⁴ Risk factors for pulmonary complications include a positive smoking history, presence of shortness of breath, or clinical evidence of chronic obstructive pulmonary disease. All elderly patients undergoing major surgical interventions should have a baseline chest radiograph. Screening spirometry can be performed to determine forced vital capacity and FEV1. A baseline arterial blood gas measurement also will help to identify hypoxemia and hypercapnia, both of which may increase postoperative complications. If abnormalities are found, perioperative use of bronchodilators and incentive spirometry may be invaluable. When possible, regional anesthetic techniques may provide excellent analgesia while helping to reduce the postoperative pulmonary complications associated with general anesthesia and endotracheal intubation.

Renal complications are also increased in elderly surgical patients in the perioperative period. Renal size and volume decrease with age, accompanied by intrarenal vascular changes. There is a decrease in the number of glomeruli and nephron mass, resulting in decreased filtration area. Serum creatinine concentration is an insensitive indicator of renal function in the elderly, however.¹⁰ The physiologic age-related changes in renal function increase susceptibility to renal ischemia as well as to nephrotoxic agents. Age-related changes in renal function result from progressive glomerulosclerosis and reduction in renal mass resulting in decreased creatinine clearance and glomerular filtration rate. This is worsened by a decline in cardiac output with increasing age and subsequent decrease in renal blood flow. It has been shown that patients with impaired glomerular filtration rate are more susceptible to volume changes that occur in the perioperative period. Furthermore, decreased drug elimination can potentiate the effects of nephrotoxic drugs and prolong the sedative effects of anesthetics and narcotic used for postoperative pain management.¹² Acute renal failure is proven to dramatically increase morbidity and mortality in elderly patients. The mortality risk of perioperative renal failure in all patients is approximately 50% and may be even higher in elderly patients. Therefore, careful management of fluid and electrolyte status is prudent to avoid imbalances and limit exposure to nephrotoxic diagnostic studies and medications in the perioperative period. Patients >70 years old may be susceptible to the nephrotoxic effects of certain anesthetic agents, and thus should be protected by hydration and diuresis, as long as they can tolerate the fluid load.¹⁰ Prompt recognition of renal compromise, marked by an elevation of blood

urea nitrogen or creatinine levels or oliguria, requires aggressive correction of underlying causes. Furthermore, electrolyte imbalances can lead to potentially devastating cardiac conduction abnormalities and arrhythmias.¹² Although not routinely advocated in younger patients, elderly patients should have routine electrolyte panels and urinalysis before all surgical interventions to identify potential renal dysfunction.¹⁵ Underlying causes of abnormalities found on screening should be corrected before surgery and may necessitate intravascular volume repletion to ensure adequate renal perfusion perioperatively.

A *functional evaluation* which includes an assessment of the cognitive level of functioning is an important part of the preoperative evaluation of elderly surgical candidates. This ensures that operative intervention will not significantly impair the quality of life of an elderly surgical candidate. The ability to withstand the stress of surgical interventions is dependent on functional reserve and the ability to build an appropriate response to peri-operative stress.¹⁰ The ability to perform ADLs such as feeding, dressing, bathing, and toileting have been correlated with postoperative morbidity and mortality (Table 47-2). Preoperative functional assessment can be measured by hand grip strength, timed "up and go," and functional reach tests⁷. All of these tests independently predicted better recovery and shorter time to recover ADLs after major surgery. In addition, these tests provide an accurate assessment of a patient's muscle mass, nutritional status, coordination, gait speed, balance, and mobility.⁵ Proper functional assessment will accurately predict rehabilitation needs, estimate biologic reserve, and indicate an enhanced risk of complications.¹⁰

The functional status of an elderly patient is directly and inversely correlated to pulmonary and cardiac complications that may ensue following surgical interventions. For example, functional impairment often leads to immobility, which can lead to increased risk of postoperative atelectasis, pneumonia, deep vein thrombosis (DVT), and pulmonary embolism. Furthermore, proper functional assessment has been shown to improve diagnostic and therapeutic outcomes as well as to lead to identification of previously undiagnosed conditions that may be treatable preoperatively or managed peri-operatively.¹⁰

Cognitive function often is overlooked in the preoperative assessment of patients, because patients are not typically formally evaluated before surgical intervention (i.e., mini-mental state examination). However, knowledge of baseline cognitive function provides invaluable information because subtle changes in cognition often herald postoperative complications, such as underlying infection. Cognitive impairment, including delirium and confusion commonly occur in the elderly patient during the early postoperative period and can result in increased morbidity, delayed functional recovery, and prolonged hospitalizations. The etiology of this postoperative cognitive dysfunction may be multifactorial. Advanced age, history of alcohol abuse, baseline cognitive disturbance, hypoxia, and hypotension have all been shown to be contributing factors.¹⁶ It is crucial that careful attention be paid to adequate postoperative analgesia to improve recovery while avoiding compromise of cognitive function. Methods such as "Beer's Criteria" are useful tools to assess whether a particular drug is appropriate for the aged patient. Finally, dementia is a known predictor of poor long-term survival.

A *formal nutritional assessment* is invaluable in the perioperative assessment of elderly patients. Poor nutritional status in elderly patients is common and results from the interplay between physiologic, psychosocial, and economic changes that accompany the aging process. Elderly patients may have poor nutritional

status because of either poor intake due to the underlying illness or pre-existing comorbid conditions. In the outpatient setting, it is estimated that 9% to 15% of persons >65 years old are malnourished. This increases to 12% to 50% and 25% to 60% in the acute inpatient hospital setting and chronic institutional settings, respectively.¹⁷ The cycle of frailty that occurs with chronic undernutrition or malnutrition can lead to progressive functional decline, loss of muscle mass, and decreased oxygen consumption and metabolic rate in this population.¹⁷ Therefore, adequate assessment of nutritional status of these patients preoperatively and the prompt institution of nutritional support is of utmost importance. This is an integral component of the preoperative assessment, considering that nutritional status is a proven independent predictor of surgical outcomes. Deterioration of a patient's nutritional state in the perioperative period contributes to adverse outcomes. Poor nutrition can lead to increased nosocomial infections, multiorgan system dysfunction, poor wound healing, and impaired functional recovery. Therefore, nutritional assessment and support, if necessary, not only give patients additional reserve to minimize postoperative complications, but aid in appropriate wound healing, functional recovery, and rehabilitation.

Protein energy malnutrition (PEM) also can result from maintaining compromised surgical patients nil per os (NPO). PEM may occur quickly in the elderly, malnourished surgical patient in a hypermetabolic state induced by stress of illness and surgery. The physiologic consequences of PEM are multiple and include anorexia, hepatic dysfunction, decreased mucosal proliferation, and sarcopenia.¹⁷ A good marker of PEM is hypoalbuminemia, also shown to be an extremely accurate predictor of surgical outcomes. The incidence of postoperative complications is increased in patients with serum albumin levels <3.5 g/L.¹⁷ Current recommendations indicate that if patients demonstrate compromise of nutritional status as defined by >10% weight loss and serum albumin level <2.5 g/dL, they should be considered for a minimum of 7 to 10 days of nutritional repletion prior to surgery.¹⁰

The significant impact of nutritional status on surgical outcomes and functional recovery in the elderly population after surgical intervention underscores the importance of an accurate preoperative nutritional assessment. In busy surgical practices, the question arises as to whether this can be done in a simple, reproducible, and cost-effective manner while obtaining vital information. There are several methods of assessing nutritional status, including anthropomorphic measures (i.e., body mass index), biochemical laboratory values (i.e., transferrin, albumin, and prealbumin), and clinical assessments.¹⁷

The Mini Nutritional Assessment (MNA) is an established, validated nutritional assessment tool which can be useful for the preoperative assessment of the elderly surgical candidate. The MNA consists of a screening portion assessing the patient's current body mass index, food intake and weight loss, mobility, and presence of stressors, depression, or dementia, all of which can exacerbate undernutrition or malnutrition in the elderly patient. The goal is to identify patients at risk for malnutrition, and who need further evaluation involving a more complete psychosocial assessment and determination of mode of feedings. This tool helps to identify undernutrition and malnutrition in older individuals, >65 years old, and helps to direct timely interventions which result in improved functional recovery.

The combined effects of poor nutrition, decreased cognition, and immune impairments due to nutritional or pharmacologic factors create a treacherous circumstance for elderly

patients with poorly defined symptoms or who present with more advanced disease. In acute abdominal conditions, such as acute appendicitis and acute cholecystitis, one third of elderly patients will lack an elevated white blood cell count, one third will lack fever, and one third will lack physical findings of localized peritonitis. These deficits contribute to a threefold higher rate of perforated appendicitis and of gangrene of the gallbladder in elderly patients compared to young patients. An "unimpressive" physical exam in an elderly patient with acute onset of abdominal symptoms should never be taken as a sign of the absence of surgical disease.

The value of the multifaceted geriatric preoperative assessment led to the formation of an expert geriatric surgery panel by the American College of Surgeons National Surgical Quality Improvement Program (ACS NSQIP) and the American Geriatric Society (AGS). The panel formulated best practice guidelines for surgery in the elderly that have been adopted as standards for training programs (see Fig. 47-2). This checklist may prove to be a useful tool in the preoperative identification of issues that may play an important role in the outcome of a surgical procedure. This not only highlights the importance of the factors described previously but also provides a tool that physicians can utilize in the nonurgent setting to institute preventative or corrective measures to help the geriatric patient maintain their quality of life. (Table 47-3)

Checklist for the Optimal Preoperative Assessment of the Geriatric Surgical Patient

In addition to conducting a complete history and physical examination of the patient, the following assessments are strongly recommended:

- ☐ Assess the patient's cognitive ability and capacity to understand the anticipated surgery.
- ☐ Screen the patient for depression.
- ☐ Identify the patient's risk factors for developing postoperative delirium.
- ☐ Screen for alcohol and other substance abuse/dependence.
- ☐ Perform a preoperative cardiac evaluation according to the American College of Cardiology/American Heart Association algorithm for patients undergoing noncardiac surgery.
- ☐ Identify the patient's risk factors for postoperative pulmonary complications and implement appropriate strategies for prevention.
- ☐ Document functional status and history of falls.
- ☐ Determine baseline frailty score.
- ☐ Assess patient's nutritional status and consider preoperative interventions if the patient is at severe nutritional risk.
- ☐ Take an accurate and detailed medication history and consider appropriate perioperative adjustments. Monitor for polypharmacy.
- ☐ Determine the patient's treatment goals and expectations in the context of the possible treatment outcomes.
- ☐ Determine patient's family and social support system.
- ☐ Order appropriate preoperative diagnostic tests focused on elderly patients.

Figure 47-2. Checklist of questions to be used during assessment of geriatric patient. This novel tool takes into consideration issues unique to geriatric patients, including frailty, cognition, and support systems. (From Chow WB et al¹ with permission from Elsevier. © 2012 American College of Surgeons.)

Table 47-3

Goals for ethical decision making in elderly surgical patient.

1. Acknowledge medical futility; physicians are not required to provide life-sustaining treatment that is deemed medically futile.
2. Clarify patients' wishes regarding life-sustaining therapies in accordance with Patient Self-Determination Act (i.e., advance directives, living wills, do not intubate/resuscitate orders).
3. Respect patient autonomy: right to accept and refuse treatment despite consequences of decision.
 - Ensure mental competency before establishing autonomy.
 - May appoint surrogate decision maker in case of incapacitation.

SPECIFIC CONSIDERATIONS**Cardiovascular**

It is estimated that approximately 40% of the projected 25 million octogenarians comprising the U.S. population by the year 2025 will suffer cardiovascular symptoms, many of whom will require cardiovascular surgical treatment.¹⁸ With advances in cardiopulmonary bypass technique, myocardial protection, and improved perioperative care, coronary artery bypass grafting (CABG) and valve replacement operations can be safely performed in elderly patients. Senile calcific aortic stenosis is common within this population, and referral for aortic valve replacement is increasing, encompassing many patients who are >75 years old. Interestingly, despite some degree of age bias in the referral of patients for major cardiac surgery, advanced age alone is not a predictor of poorer outcomes or increased mortality compared to younger patients. It has been demonstrated that emergency operations, preoperative New York Heart Association (NYHA) functional class 3 or greater, and chronic renal failure were the main predictors of increased operative mortality, but not patient age, per se.¹⁸ In one study, preoperative renal dysfunction, cerebrovascular disease, valve surgery, and catastrophic state were independent predictors of increased mortality in elderly patients.¹⁹ Elderly patients with nondialysis-dependent renal dysfunction had a 60% chance of death during a 5-year follow-up period compared to 25% in elderly patients without a history of renal dysfunction. Similarly, the presence of cerebrovascular disease resulted in a two-fold increase in mortality among elderly patients.¹⁹ Even patients who were 80 years of age or more did not have any significant increase in surgical risk and within this population, the 4-year actuarial survival was 70.5% with an event-free survival of approximately 60.6%.¹⁹

There has been an increase in definitive operative intervention to elderly patients requiring CABG. Although older patients have higher morbidity and mortality rates after cardiac surgery than do younger patients, these rates are decreasing. The Society of Thoracic Surgeons reports that perioperative mortality rates range from 1.6% in patients 51 to 60 years of age to 7.7% in those 81 to 90 years of age.²⁰ This decline in morbidity and mortality rates likely reflects better preoperative assessment and patient selection. Furthermore, this decline has occurred despite the advancing age of cardiac patients at time of referral, advanced disease, and greater comorbid disease burden. Elderly patients are more likely to have significant triple-vessel disease accom-

panied by poor ejection fraction, left ventricular hypertrophy, significant valvular disease, and previous history of myocardial infarction than are younger patients.²⁰ Elderly patients also are more likely to be classified as NYHA functional class 3 or higher and are more likely to present on an emergent basis, in part because of reluctance to provide elective surgical intervention because of presumptive poorer outcome. Despite the increased risk of morbidity and mortality compared to younger patients, elderly patients, including those >80 years old, can undergo CABG with acceptable mortality risk. The overall mortality rate is approximately 7% to 12% for elderly patients, including those in whom CABG is performed under emergency conditions. The mortality rate decreases to approximately 2.8% when CABG is performed electively with careful preoperative evaluation.²¹

Valve Replacement

There also is an increasing percentage of the geriatric population who present with symptomatic valvular disease requiring intervention. The most common valvular abnormality present in elderly patients is calcific aortic stenosis, which can lead to angina and syncope.²² The operative mortality from aortic valve replacement is estimated to be between 3% and 10%, with an average of approximately 7.7%.²⁰ If aortic stenosis is allowed to progress without operative intervention, CHF will ensue. The average survival of these patients is approximately 1.5 to 2 years. If a patient is a candidate for operative intervention, age should not be a deterrent, especially considering the potential to increase life expectancy. It has been recommended that the carefully selected, minimally symptomatic octogenarian with aortic stenosis should be considered a low-risk patient and be expected to experience an uneventful operative course and expedient recovery. More importantly, if elective procedures are delayed until symptoms or left ventricular dysfunction develop, patients may suffer from unnecessary increased operative risk and mortality.¹⁸ Early intervention results in a demonstrable improvement in quality of life in these patients, with many improving their NYHA functional classification.

Elderly patients require surgery for mitral valve disease when ischemic regurgitation is present. Surgery for mitral valve disease carries a higher morbidity and mortality risk than for aortic intervention, with an estimated mortality rate as high as 20%.²⁰ Left ventricular function usually is compromised in patients requiring intervention, leading to a poorer outcome in these patients. The surgical outcome for mitral valve procedures depends on the extent of the disease, age of the patient, presence of pulmonary hypertension, and extent of coronary artery disease. The presence of comorbid conditions combined with the emergent nature of surgery in a large percentage of elderly

5▶ patients further worsens the outcome. Therefore, a decision regarding management of mitral valve disease should be individualized to each patient with the previously mentioned below factors considered. Another concern regarding elderly patients who require surgery for valve disease is the additional requirement for coronary revascularization. This increases the morbidity and mortality from surgical intervention. An elderly patient with many comorbid conditions in need of a combined procedure should only have critically stenosed vessels bypassed.²² Therefore, advanced age is not a contraindication to performing combined procedures; however, a higher mortality rate should be expected. Neurologic complications from valve surgery are particularly common in elderly patients. It has been estimated that approximately 30% of patients >70 years old who undergo valve procedures develop either transient or permanent

neurologic dysfunction.²² This often is a result of embolism from debris dislodged from the valve during the procedure or from a formed thrombus in the right atrium.

An important consideration in valve replacement procedures in elderly patients is the type of prosthesis to be used. Elderly patients are at increased risk from bleeding-associated anticoagulation complications. This is especially significant in patients who have experienced falls and minor trauma that have resulted in intracranial hemorrhage. To avoid the lifelong requirement for anticoagulants, bioprosthetic valves should be used in place of mechanical valves whenever possible.²² Although the bioprosthetic valves are not as durable as mechanical valves, studies demonstrate excellent structural integrity 10 years postprocedure, making it an appropriate choice in an elderly patient.

Cancer

The incidence of most cancers is age dependent, and the expanding aged population is rapidly increasing the number of elderly patients who require multimodal therapy for various oncologic diseases, including lung, breast, pancreas, esophagus, stomach, and colorectal malignancies. Approximately 50% of cancer diagnoses are currently made in patients aged 70 years or older.¹⁰ It is predicted that the increase in the elderly population will account for up to a 50% increase in the number of patients undergoing oncologic procedures by the year 2020. The increased life expectancy of the geriatric patient coupled with the increasing incidence of cancer with advancing age will lead to an increased prevalence of

malignant disease requiring surgical intervention. This is an area of great interest given that randomized clinical trials to determine the outcomes of elderly patients undergoing curative resections, as well as neoadjuvant and adjuvant therapy, are lacking. In addition, elderly patients are rarely included in clinical trials; therefore, treatment decisions are often based on individual surgeon experience and non-geriatric data, and may be flawed by inherent biases regarding the outcome of complete oncologic resections in elderly patients. Surgeons may also be reluctant to expose older patients to the toxic effects of chemotherapy and radiation without proven efficacy in this geriatric population. This highlights the need for research targeting the specific needs of elderly patients with malignancy to aid in the development of specific treatment guidelines for various cancers within this age cohort.

Currently, the geriatric population is undertreated for malignant diseases and does not receive curative resections or adjuvant therapies afforded to same-stage younger patients.¹¹ Potential reasons include poorer functional status compared to younger patients, patient and family preference, age bias, life expectancy, and concerns regarding quality of life after major operative interventions.²³ Surgeons will be challenged to decide whether major surgery is justified in elderly patients, especially those with limited life expectancy. Effectiveness of oncologic surgery in elderly patients depends on whether a cure can be achieved safely without compromise to functional status or quality of life. Postoperative life expectancy should be improved by surgery, or, at the very least, not diminished. A useful treatment algorithm is provided in Fig. 47-3. A study undertaken

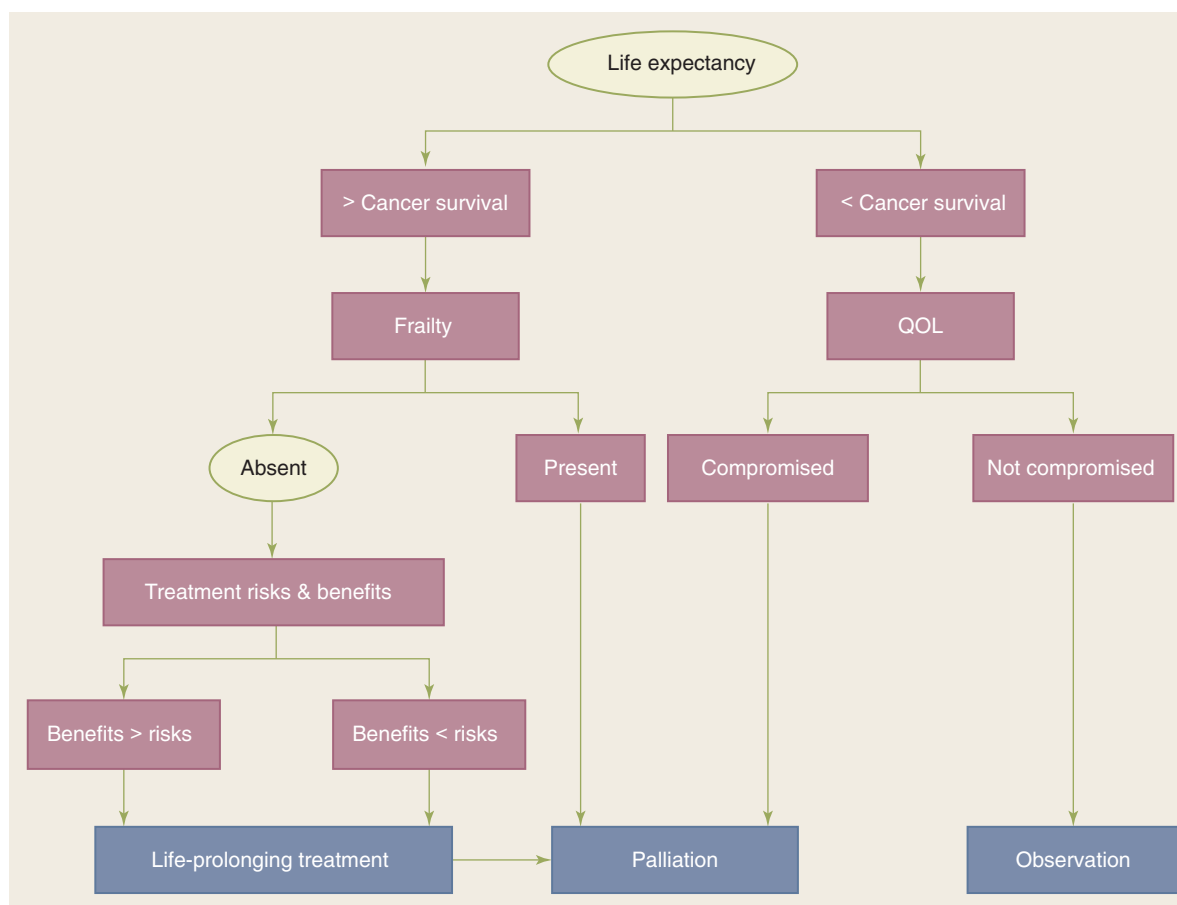


Figure 47-3. A useful treatment algorithm to illustrate the effectiveness of oncologic surgery depends on the balance between achieving cure and maintaining functional quality of life (QOL). (Reproduced with permission from Balducci L, Beghe C. *Cancer Control. Journal of the Moffitt Cancer Center.* 1999; 6:466.)

using the Surveillance, Epidemiology and End Results database assessing cancer-directed surgery (CDS) for localized disease for solid malignancies found that the rates of CDS declined with increasing age for all cancers, especially noted for the aged elderly >70 years old. In addition, CDS was less likely to occur with patients found to have lung, esophagus, stomach, liver, or pancreatic cancer. A careful assessment of the general and cancer-related condition of the patient is crucial to planning the best surgical intervention and postoperative adjuvant therapy.

Formulating a comprehensive, multimodal treatment plan for an elderly patient with a malignancy amenable to surgical intervention is based on careful consideration of the patient's expected life span, specifically if the life span is expected to exceed survival from the malignancy. Additionally, considerations include the patient's ability to tolerate the surgery and any complications that may ensue, as well as the likelihood that the patient would suffer a complication from the cancer which would adversely impact quality of life.²⁴ An ongoing international study that is titled "Preoperative Assessment of Cancer in the Elderly (PACE)" is designed to evaluate a scoring system that aids in assessing the oncogeriatric patient for surgical intervention. The PACE study incorporates several validated instruments that assess the functional and physiologic status of patients, including the Mini Mental State Examination, capacity to perform ADLs, Geriatric Depression Scale, and the ASA classification among other useful instruments. Interestingly, the PACE assessment also includes The Physiological and Operative Severity Score which has been shown to predict morbidity and postoperative mortality in general surgery and in patients with lung and colorectal malignancy. This score includes the age of the patient and gives consideration to operative factors, including the type of surgical procedure used, the presence and extent of malignancy, and the timing of the operation (i.e., planned elective procedure or an emergency intervention).¹⁰ Palliative interventions are a part of the therapeutic armamentarium; however, a surgeon must weigh these variables carefully to determine which surgical intervention (i.e., palliative vs. curative) is appropriate.

Breast Cancer

It is projected that there will be a 72% increase in the number of elderly women diagnosed with breast cancer in the United States by 2025. Furthermore, 50% of breast cancers occur after the age of 65 years old and 25% after the age of 75 years old.²⁵ The estimated risk for development of new breast cancer is one in 14 women aged 60 to 79 years old compared to one in 24 in women aged 40 to 59 years old.²⁵ Mortality rates following breast cancer surgery in elderly women is <1%, and therefore, surgical interventions remain the cornerstone of therapy for breast cancer in elderly women. However, as expected, the presence of comorbid conditions affects clinical outcomes in elderly patients with breast cancer. A recent study demonstrated the presence of comorbid conditions in patients with breast cancer rose to as high as 55% in patients >80 years of age, with cardiovascular disease, diabetes, and previous cancer being most common.²⁶ As expected, the resulting 5-year survival rate was lower in patients with two or more comorbid conditions.

A recent study on risk factors for breast cancer in patients >75 years of age showed similarity to younger women and included obesity, nulliparity, family history, and advanced age at menopause.²⁷ Interestingly, although breast cancer presentation in elderly patients may be diagnosed at more advanced stages, both clinical and pathologic data demonstrate less aggressive disease

in elderly women with more favorable biologic characteristics. Elderly breast cancer patients are more likely to have estrogen-positive tumors and increasing endocrine responsiveness.²⁷ Despite these relative advantages, a large number of elderly women are not offered conventional therapies for breast cancer. Moreover, elderly patients who are offered breast conservation surgery for breast cancer are less likely to have axillary dissection, postoperative radiation, and chemotherapy. This will undoubtedly influence surgical outcomes in elderly patients with breast cancer considering that local recurrence rates after conservative surgery without radiotherapy are reported as high as 47%. Advancing age has been demonstrated to be an independent predictor of nonconcordance with treatment guidelines for definitive surgical therapy and adjuvant chemotherapy, as well as hormonal therapy. One study demonstrated that the odds of receiving a recommendation for chemotherapy decreased by 22% for each year of advancing patient age.²³ The nonsurgical management of breast cancer in elderly patients is falling out of favor because there is currently no rationale for denying surgical therapy for elderly breast cancer patients. Surgery and hormonal therapy were the best options for overall survival, breast cancer-specific survival, and disease-free survival. A Cochrane Review concluded that treatment with tamoxifen alone is not an acceptable option because of higher local progression of disease; 81% compared to 38% with surgical intervention. Furthermore, the response rate only lasts for approximately 18 to 24 months.²³ The final conclusion is that surgery remains the standard of care for elderly patients with breast cancer. Alternative therapies should be reserved for patients who have multiple comorbid conditions leading to poor candidacy for operative intervention, those who are frail, or those who refuse surgery.

A timely study comparing the mortality after breast-conserving surgery (BCS) alone, BCS plus radiation therapy, mastectomy, and the receipt of adjuvant tamoxifen in elderly breast cancer patients confirmed that less than standard treatment for these patients resulted in increased mortality. Elderly women receiving BCS without radiotherapy have more than twice the rate of breast cancer mortality compared to women undergoing mastectomy. In addition, in older women with estrogen receptor and progesterone receptor positive tumors receiving tamoxifen, the rate of breast cancer death increased substantially with the decreasing duration of tamoxifen use.²⁸ The standard of treatment for elderly patients with breast cancer should be the same as younger patients; BCS plus radiotherapy when indicated. If patients decline postoperative radiotherapy or are medically unfit for radiotherapy, mastectomy should be performed. Furthermore, elderly patients with tumor size <2 to 3 cm and no clinical evidence of axillary involvement should be offered sentinel node biopsy.²⁹

One of the most interesting controversies surrounding breast cancer in elderly women is the appropriate age limits of screening. A retrospective study demonstrated a decline in cancer-related mortality among women who underwent regular screening mammography up to 75 years of age.²⁷ Women who underwent at least two mammographic examinations between the ages of 70 and 79 years experienced a two-and-one-half-fold reduction in breast cancer mortality compared to elderly women who did not undergo screening.²³ The screening benefits depend on life expectancy. In women with multiple comorbidities, the decision to perform screening should be based on estimated life expectancy. People with <5 years of life expectancy are unlikely to benefit from screening. The American Geriatric Society recommends that screening should be individualized rather than set by age-specific guidelines. The current recommendation is that

no upper age limit for screening be set as long as the estimated life expectancy is 4 or more years.

Colorectal Cancer

The incidence of colorectal cancer (CRC) increases with advancing age, similar to most other malignant conditions. Approximately 90% of cases of CRC are diagnosed in patients >55 years old.³³ Of concern is the increased postoperative morbidity and mortality following extensive surgical resections in elderly patients, with a significant increase in patients >70 years old. In fact, in-hospital mortality for patients >85 years old undergoing surgery for colorectal malignancy is estimated to be nine-fold greater than for younger patients.³⁰ Furthermore, elderly patients often have decreased cancer-specific survival compared to younger patients. It has been proven that the 5-year cancer-specific survival for CRC is similar among the age cohorts. Therefore, age is not an independent factor accounting for the decreased survival among elderly patients. It is rather a consequence of comorbid conditions and impaired physical capacity necessary for recovery from perioperative physiological stress.³⁰ This leads to bias regarding poorer outcomes in elderly patients. For this reason, many elderly patients are receiving suboptimal cancer therapy and limited resections resulting in decreased survival rates and poorer outcomes. With the ever aging population, this must be addressed and clinical modifications implemented to improve outcomes of elderly patients undergoing surgical interventions for colorectal malignancies. Elderly patients should have continued, aggressive screening for colorectal malignancy and strict adherence to accepted surgical and adjuvant treatment guidelines.

One of the most important aspects to delivering appropriate care to elderly patients with CRC is to consider the patient's wishes as well as expectations from the surgical intervention. In this respect, functional outcomes and quality of life take precedence in treating elderly patients, especially the aged elderly. Of patients >75 years old who underwent elective surgery, few demonstrated protracted decline in ADLs and most experienced significant improvement in quality of life.³¹ Approximately 10% of elderly patients >80 years old have protracted postoperative disability. Estimation of physical ability and surgical stress is useful for predicting decline in ADLs and postoperative disability. It has been shown that, in patients <80 years of age, a complete resection for cure is most important, whereas in patients >80 years old, avoidance of a stoma becomes paramount. These are important considerations for the geriatric surgeon.³⁰

A prospective study was recently undertaken to specifically evaluate the epidemiology and risk of surgical intervention for CRC in elderly patients. A large cohort of 47,455 patients was divided based on age <75 years old and >75 years old.³⁰ It was determined that a significant portion of elderly CRC patients are female, with multiple comorbidities leading to advanced ASA levels of 3 and above. The study determined that elderly patients underwent surgical interventions less often than younger patients (81% vs. 88%, respectively, $P < .001$), more frequently required urgent or emergency operations, and were more likely to have operative procedures in which the primary cancer was not resected. Obstructive tumors are significantly more common in patients >70 years old, and elderly patients are still presenting far too commonly with surgical emergencies resulting from obstruction and perforation in up to 40% of the cases.¹¹ In addition, elderly patients had higher postoperative mortality than younger patients (10.6% vs. 3.8%, respectively). Right colectomies, Hartmann's procedures with colostomy,

transanal endoscopic microsurgery, and transanal resection of tumors were more common in elderly patients, whereas formal resections, including low anterior and abdominoperineal resections, were more common in younger patients.³⁰ Elderly patients are less likely to undergo CDS; with each half a decade increase in age >70 years old, the odds of receiving cancer-directed surgery were reduced by 44%. Interestingly, many of these patients presented with lesions of lower-stage Duke's cancer classification. However, this was not secondary to earlier presentations as one might assume, but rather secondary to understaging from surgical treatment. Accurate staging may not be possible with local resections, limiting the number of lymph nodes available for proper staging.³² Elderly patients also are less likely to undergo preoperative irradiation and neoadjuvant chemotherapy, reducing the likelihood of curative resection.³⁰

Liver resection for CRC liver metastases in properly selected elderly patients 70 years of age or greater is feasible with older patients having similar operative survival to younger patients. Palliative surgery remains a viable option for elderly patients with disseminated CRC and should be aimed at the reduction of symptoms such as pain, obstruction, or hemorrhage. Bowel obstruction can be relieved with intestinal bypass or a diverting colostomy. The most common site of disseminated disease is the liver, and uncontrolled liver metastases are responsible for pain, abdominal distention, jaundice, and inferior vena caval obstruction. Elderly patients with metastatic disease who are not candidates for curative resection may be considered for ablation of the lesions by local destruction, cryotherapy, or radiofrequency ablation. More traditional means such as chemotherapy, which can be administered via the hepatic artery or radiation, also may be used.³³

Similar to breast cancer, an upper age limit for CRC has not been clearly established. Screening for CRC may not lead to an observed survival benefit until 5 years or longer after screening had occurred. This would limit the benefit of screening in aged populations with limited life expectancy. An interesting way of looking at this controversy is from a recent study that determined that the number of screening colonoscopies needed to prevent one CRC-related death (the number necessary for survival or NNS) increased as with increasing age and comorbidities. For example, in healthy men and women aged 75 to 79 years old, the NNS was 50. The corresponding NNS in patients 90 years and older was 279 in women and 482 in men.³⁴ Consideration for continued screening in very elderly patients should take into account age and predicted life expectancy, comorbid burden, expected duration of the protective effect of screening, risk for cancer, results of previous screening colonoscopies, and patient preference.³⁴

Lung Cancer

Lung cancer is the leading cause of cancer-related deaths in the United States for patients >70 years old. National Cancer Institute statistics show that the peak incidence of lung cancer is between 75 and 79 years of age. Elderly lung cancer patients also have a higher mortality rate, and therefore, the peak mortality rate is between ages 75 and 84 years.³⁵ Non-small cell lung cancer accounts for roughly 80% of all lung cancer cases, and >50% of these patients are >65 years of age. Interestingly, approximately 30% of these patients are 70 years or older at diagnosis.³⁶ Lung cancer is highly prevalent among elderly patients, so much so that a 2-cm, asymptomatic, solitary pulmonary nodule in a 70-year-old male smoker has a >70% chance of being an occult lung cancer. Squamous cell carcinomas are more common among elderly patients than among younger

patients, and these tumors are associated with a higher incidence of local disease, tend to have lower recurrence rates, and have longer survival times than nonsquamous cancers.³⁵ In cases of resectable primary lung cancer, surgery remains the treatment of choice independent of age.¹¹

The estimated life expectancy of untreated lung cancer is approximately 9 months. This can increase to as high as 18 months with palliative chemotherapy and radiation. However, the life expectancy of an elderly patient who has undergone a successful operative resection is estimated to be as high as 31 months, making this the preferred option when feasible.¹³ However, despite this and the fact that more elderly patients present with stage I disease, elderly patients are offered curative surgery less frequently than younger counterparts. The same holds true for chemotherapy and radiation.

Advanced age is an independent risk factor for death after thoracotomy, with significantly increased mortality after age 65. These reasons are multifactorial partly due to the physiologic debilitation that occurs with division of the intrathoracic muscles that aid in respiratory function and the loss of lung volume after resections.¹³ One study demonstrated that patients 70 years of age or older who underwent thoracotomy for lung cancer had an operative mortality rate of 14%, which is directly related to the extent of the pulmonary resection. In one of the largest prospective, multi-institutional trials conducted, The Lung Cancer Study Group, increasing age led to a significant increase in 30-day mortality for patients undergoing thoracotomy and lung resection.¹³ They found overall mortality to be approximately 3.5% in patients <65 years old, which rose to 7.3% for patients 70 years or older and as high as 8.1% for octogenarians. However, with improved surgical options, including minimally invasive video-assisted thoracic surgery (VATS) in the past decade, the mortality rate has ranged from 3% to 5% in carefully selected patients.² In a recent study conducted to determine if VATS resulted in lower morbidity in the elderly population in comparison to open, rib-spreading thoracotomy, the overall morbidity for minimally invasive surgery was 28%; this increased to 45% with traditional open procedures.³⁶ Furthermore, elderly patients undergoing VATS tended to have less severe complications compared to patients undergoing thoracotomy.³⁶ Limited resections (segmentectomies) may be a consideration in elderly patients with limited life expectancy or poor cardiac and pulmonary reserve who may not tolerate a more extensive procedure. Some studies have shown that limited resections may provide a comparable survival rate to lobectomies in elderly patients as long as the resection includes all foci of tumors and provides a microscopically free margin. The most striking finding was that any survival difference between treatment modalities disappeared after 71 years of age. Interestingly, even smaller resections such as VATS and wedge resection may be a viable oncologic option in an elderly patient with resectable disease but limited life expectancy.¹³ This is limited to very small tumors <7 mm in diameter and not yet proven to be clinically efficacious. Of particular interest is that VATS procedures may result in lower rates of postoperative confusion in elderly patients and this may be secondary to the decreased physiologic stress of minimally invasive procedures, faster recovery rates, and decreased narcotic requirement for pain control.¹³ Careful preoperative selection and optimization combined with aggressive postoperative care and rehabilitation make surgical intervention for resectable disease feasible in aged populations.

Trauma

Patients >65 years of age currently account for approximately 23% of total hospital trauma admissions—many of which are multisystem and life threatening.³⁷ Geriatric trauma will continue to challenge surgeons in understanding the physical and physiologic impact of various mechanisms of injury, the need for careful assessment of comorbid conditions with particular attention to medication regimens, the rehabilitative capacity of an elderly trauma patient, and the knowledge of specific interventions that help to minimize morbidity and mortality in this population following traumatic injury.

The current geriatric population has fewer disabilities and is considerably more active than previous generations, which predisposes them to traumatic injuries. The most common type of trauma is blunt injury resulting from falls and motor vehicle collisions or pedestrian accidents. Falls currently account for 20% of severe injuries in elderly patients. Many underlying chronic and acute diseases common to elderly patients place them at increased risk for falls. These diseases include postural hypotension, leading to syncopal “drop attacks”; dysrhythmias from sick sinus syndrome; autonomic dysfunction; polypharmacy with improper dosage of antihypertensive and oral hypoglycemic agents resulting in hypotension; and hypoglycemia, respectively.³⁸

Elderly patients also can fall victim to penetrating trauma, especially in elderly patients who may have underlying depression and suicidal ideations or are victims of elder abuse. It is estimated that approximately 40% of all trauma patients by 2050 will be >65 years old.³⁹ With the expanding elderly population, this will be an increasing source of morbidity and mortality; the risk of death after major trauma with multi-system and life-threatening injuries rises steeply after age 45 years old and doubles by age 75 years old. In contrast to what is observed for abdominal and thoracic surgery, even after controlling for injury severity and pre-existing medical conditions, patients aged 65 years and older sustaining traumatic injury were 4.6 times more likely to die than younger patients.³⁹ Of note, there are several interesting aspects of care of the acutely injured elderly patient that must be kept in mind. First, physiologic reserve can be challenged by trauma. For example, previously unknown disease such as cardiac impairment may be acutely unmasked. Secondly, medications common to elderly patients, such as beta blockers and anticoagulation, cannot only inhibit the physiologic response to stress but may even worsen injury. Finally, elderly patients with impaired functional status posttrauma are more likely to lose their ability to function independently without the support of a nursing home.

Elderly patients are particularly susceptible to trauma due to changes that occur with aging, specifically, gait instability, decreased hearing and visual acuity, presence of confusion or dementia, underlying comorbid conditions, and poor to tolerate the physiologic stress of traumatic injuries. Pre-existing medical conditions increase the risk of death after trauma significantly (up to three-fold).³⁷ This is worsened when combined with an elderly patient's decreased functional reserve for handling physiologic abnormalities accompanying major trauma, such as hypotension and hypoxia. It is important to consider a trauma patient's age, as patients aged 65 to 80 years old have a 6.6% overall mortality rate after traumatic injury, which rises to 10% in patients 80 years or older.⁴²

Despite the increased risk of morbidity and mortality after traumatic injury, it is interesting to note that there is currently an undertriaging of elderly patients to level I trauma centers despite high injury severity scores.³⁹ In one study, elderly patients >65 years old were five times more likely to be

undertriaged to nondesignated trauma hospitals than younger counterparts.³⁹ However, a reduction in morbidity and mortality and posttraumatic complications as well as faster rehabilitation can result from better triaging practices. In one particular study involving acutely injured octogenarians with injury severity scores between 21 and 45, in-hospital survival was as high as 56% in trauma centers, and this dramatically decreased to 8% in those treated at nontrauma hospitals.³⁹

It is important to determine the medication regimen of elderly trauma patients. Medications such as beta blockers, calcium channel blockers, diuretics, and afterload reduction agents may impair critical augmentation of myocardial function in trauma patients, especially if they are hypovolemic. Approximately 20% of the elderly population with coronary artery disease and 10% of those with hypertension are currently on beta blocker therapy.³⁹ Therefore, tachycardia, one of the most valued signs of continued hypovolemia from either ongoing blood volume loss or underresuscitation, is lost in the elderly patient on beta blocker therapy. This makes interpretation of hemodynamic parameters in elderly patients inaccurate and, at times, misleading, which could lead to delays in appropriate interventions and resuscitation. However, it is important to keep in mind that, to date, evidence supporting early hemodynamic monitoring in elderly patients is lacking.

The other medication class that can be detrimental to an elderly, acutely injured patient is anticoagulation, ranging from aspirin and clopidogrel (Plavix) to warfarin, which may, at times, be supratherapeutic. Massive intracranial hemorrhages resulting from minor falls from standing in elderly patients are demonstrated in Fig. 47-4. Warfarin therapy may be used

in patients with atrial fibrillation, DVT, and prosthetic heart valves. The mortality rate of elderly patients on warfarin with a traumatic intracranial hemorrhage was 48% compared with 10% in an age-matched cohort not on anticoagulation therapy; it is unknown for the newer factor Xa inhibitors.³⁹ One of the most important caveats to treating elderly patients on anticoagulation with blunt head injury is the potential for significant, life-threatening intracranial hemorrhage despite initial normal head (computed tomography) CT scans. In one study, >70% of patients with minor mechanisms and negative CT scan, admitted for observation subsequently, clinically deteriorated within 12 hours of admission with a Glasgow Coma Scale of <10 and were subsequently found to have significant intracranial hemorrhages.³⁹ Therefore, prompt reversal of anticoagulation, particularly if supratherapeutic, is warranted to reduce morbidity and mortality following blunt head injury. In addition to increased risk of mortality in elderly patients sustaining blunt head trauma, a significant portion fail to resume functional independence after traumatic injury. It is estimated that approximately 20% to 25% of elderly trauma patients require discharge to a skilled nursing facility for long-term care and rehabilitation.³⁷ Poor functional outcome has been attributed to several factors among which are age >75 years old, presence of shock on admission, severe head injury, and development of infectious complications.

MINIMALLY INVASIVE SURGERY

Laparoscopy

Open abdominal procedures may require more intensive postoperative care, longer hospital stays, and an increased need for postoperative rehabilitation and possible institutionalization for elderly patients with limited reserve. However, the increasing experience with laparoscopic techniques, combined with minimized pain, decreased length of hospital stay, and low morbidity and mortality rates, has led to the increased use of minimal access procedures among elderly patients. It has expanded from cholecystectomies to more complex procedures, including colon resections, gastrectomies, and cardiac surgery.

Minimally invasive laparoscopic surgery reduces common postoperative complications such as atelectasis, gastrointestinal ileus, and wound infections. In elderly surgical patients, these complications easily progress to pneumonia, DVT, and metabolic and electrolyte disturbances.⁴⁰ Decreased postoperative pain from smaller incisions leads to faster return to a preoperative level of functioning, including early ambulation, which decreases complications from prolonged bed rest, such as DVT and pneumonia from compromised pulmonary mechanics. The latter is especially important for elderly patients because deconditioning occurs with long hospital stays, which depresses their ability to return to preoperative functional status. Laparoscopic surgery also provides the added benefit of reduction of the inflammatory, hormonal, and metabolic stress induced by major open surgical operations. The net result is that patients who undergo laparoscopic procedures may do better; in colon

6 ▶ surgery it has been shown to increase the chance that the patient returns home over an interim rehabilitation center.

However, these benefits must be balanced against the potential adverse effects of carbon dioxide (CO₂) insufflation and hemodynamic alterations induced by pneumoperitoneum and increased intra-abdominal pressure with concomitant decrease in venous return.⁴¹ Therefore, decisions to perform minimal access procedures in the elderly must be individualized to the patient

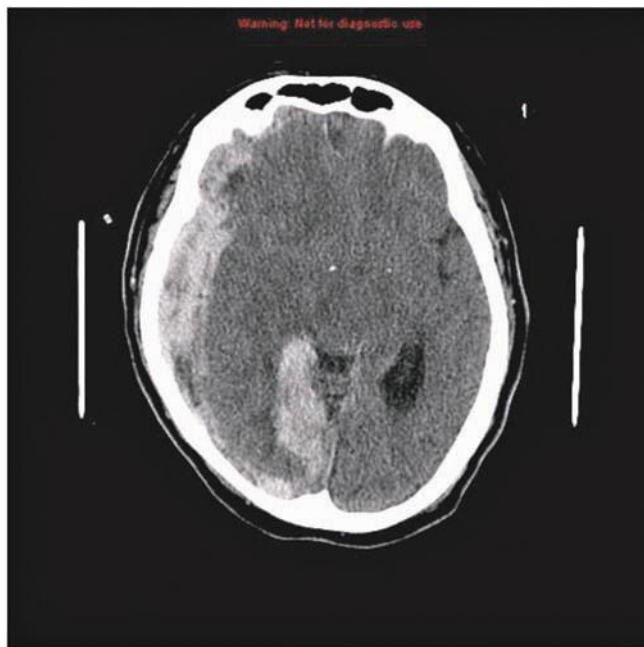


Figure 47-4. Massive intracranial hemorrhage resulting from seemingly minor trauma. An 86-year-old patient fell from a standing position and presented to the emergency room with six hours of injury with a Glasgow Coma Scale of 5 and a blood pressure of 167/55. She was on aspirin and clopidogrel therapy for ischemic heart disease, along with 14 other medications for congestive heart failure, diabetes, and hypertension. She expired from her intracranial wounds. (Photo used with permission of Dany Westerband, MD, Suburban Hospital, Bethesda, MD).

with careful consideration of the impact of comorbid conditions and the potential for poor cardiopulmonary reserves. This helps to provide the optimal circumstance for intervention resulting in improved surgical outcomes.

It is important to consider using a reduced intra-abdominal insufflation pressure during a laparoscopic procedure in an elderly patient. Pressures up to 20 mmHg are associated with increased filling pressures and cardiac output. However, further increased elevations result in decreased central venous pressures and cardiac output, which can be life threatening in a patient with preexisting cardiac dysfunction and poor functional reserve.

Studies have demonstrated that both advanced age >70 years old and an ASA classification of 3 or 4 are associated with higher conversion rates for laparoscopic cholecystectomy to open cholecystectomy.⁴² These additional challenges, however, are not a contraindication to attempting the less invasive approach because conversion to an open procedure does not adversely impact the overall morbidity and mortality of the patient.

A particularly useful application of minimally invasive techniques is to rule out a surgical abdomen in an elderly patient presenting with acute abdominal pain. Vague, poorly localized pain, further obscured by several underlying confounding comorbid conditions, as is the case with ischemic colitis and mesenteric ischemia, may subject an elderly patient with poor reserve to the risk of general anesthesia and a negative exploratory laparotomy (Fig. 47-5). Analysis of several studies directed at the application of laparoscopic techniques for the patient with acute abdominal pain demonstrated that approximately 41% had pathology necessitating open laparotomy, 10% had pathology amenable to laparoscopic intervention (i.e., acute cholecystitis), and 48% had nonsurgical disease that was subsequently managed nonoperatively, avoiding a negative exploration.⁴² Therefore, laparoscopic evaluation of abdominal pain in the critically ill elderly patient may prove to be a valuable tool.



Figure 47-5. Diagnostic laparoscopy in an 80-year-old patient with abdominal pain, elevated white blood cell count and signs of bowel obstruction and sepsis. Comorbidities included severe aortic stenosis. Findings included a localized segment of bowel which was necrotic, associated with an adhesive band. The rest of the small intestine and colon were inspected, all of which were viable. A local resection was performed, and the patient recovered quickly.

Endovascular Surgery

Abdominal aortic aneurysm (AAA) is a disease that primarily affects the elderly male patient. With increasing use of screening abdominal CT scans and ultrasounds for evaluation of various abdominal complaints, AAAs are being identified with greater frequency, most of which are diagnosed in elderly patients, given the increased prevalence of AAA with increasing age. In fact, the percentage of AAA rises from about 1% at age 55 to 60 years to approximately 10% in patients 80 years of age or older.⁴³ Elderly patients, and octogenarians in particular, were deemed poor operative candidates for the traditional open repair given the frequent presence of comorbid conditions and limited cardiopulmonary reserve to tolerate a major operation or the many hours of required operative time and general anesthesia. Elderly patients had an increased perioperative morbidity and mortality following open aortic surgery in comparison to younger cohorts. However, the introduction of endovascular techniques for repair of AAA has shifted the risk-benefit ratio for operative intervention, allowing greater life expectancy for the elective repair of this potentially life-threatening condition with the benefits of minimally invasive techniques as previously described.

Studies have demonstrated that endovascular aortic repair (EVAR) is feasible and efficacious in elderly patients, including those previously considered unfit for open repair. EVAR is a minimally invasive technique in which a prosthetic graft is introduced into the aortic lumen via the common femoral artery to exclude the aortic aneurysm sac. EVAR significantly reduces operative and anesthesia times, blood loss, intensive care needs, length of stays, and major postoperative morbidity associated with open AAA repair. The most common complication following EVAR in elderly patients is renal impairment. Typically, patients are discharged 1 to 2 days following surgery and the graft is deployed via small bilateral groin incisions, obviating the need for a major laparotomy incision. Figure 47-6 demonstrates the endovascular repair of AAA and right iliac artery aneurysm via bilateral groin access in an 82-year-old man who was discharged from the hospital on postoperative Day 2. This procedure also can be done using epidural anesthesia for high-risk candidates who may tolerate general anesthesia poorly. Endovascular repair has even been described under local anesthesia in patients at extreme high risk of rupture and death or after rupture and hemodynamic instability, precluding the ability to tolerate general anesthesia.⁴⁴

Careful consideration of the life expectancy and the risk of rupture dictate the necessity for intervention. EVAR remains a viable option in elderly patients. Nonoperative management is justified in frail elderly patients with multiple comorbidities and reduced life expectancy whose operative risks outweigh the risk of rupture and in those who are unlikely to survive long enough to benefit from the repair.

THYROID SURGERY

The prevalence of thyroid disease increases with advancing age. The etiologies, risk factors, and presentations of thyroid disease are similar across all ages, and therefore, are not discussed in detail. Of note, however, is that elderly patients more often present with cardiac manifestations of hyperthyroidism, such as atrial fibrillation, than do their younger counterparts. A common finding requiring evaluation in elderly patients is

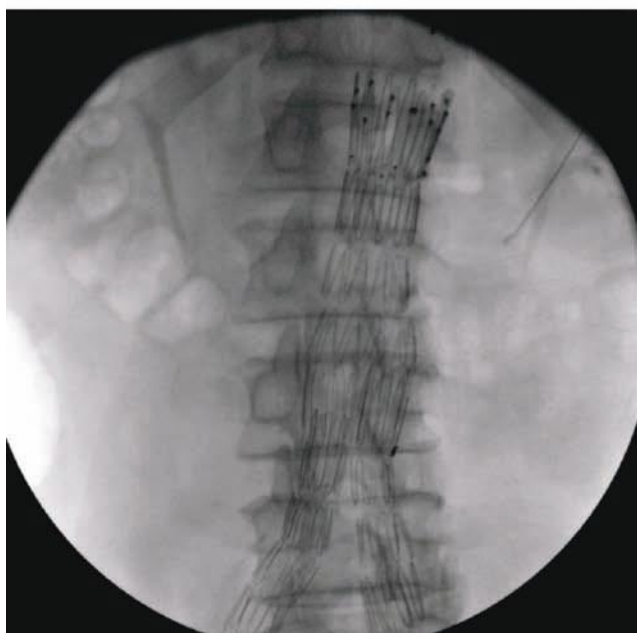


Figure 47-6. Endovascular repair of abdominal aortic aneurysms (AAAs) is gaining favor for suitable elderly patients to prevent rupture. Through minimal groin incisions, this 82-year-old patient underwent repair of an AAA and right iliac artery aneurysm and was discharged on postoperative day 2.

the presence of a thyroid nodule, usually detected by physical examination. These nodules usually are single and four times more common in women, making them a particular concern for postmenopausal elderly women. Papillary carcinoma in elderly patients tends to be sporadic with a bell-shaped distribution of age at presentation, occurring primarily in patients aged 30 to 59 years old. The incidence of papillary carcinoma decreases in patients >60 years of age.⁴⁵ However, patients >60 years of age have increased risk of local recurrence and for the development of distant metastases. Metastatic disease may be more common in this population secondary to delayed referral for surgical intervention because of the misconception that the surgeon will be unwilling to operate on an elderly patient with thyroid disease. Age is also a prognostic indicator for patients with follicular carcinoma. There is a 2.2 times increased risk of mortality from follicular carcinoma per 20 years of increasing age.⁴⁶ Therefore, prognosis for elderly patients with differentiated thyroid carcinomas is worse compared to younger counterparts. The higher prevalence of vascular invasion and extracapsular extension among older patients is, in part, responsible for the poorer prognosis in geriatric patients. Advancing age leads to increased mortality risk for patients with thyroid cancer and is demonstrated by the AMES (*age, metastases, extent of primary tumor, and size of tumor*) classification system developed by the Lahey Clinic.

PARATHYROID SURGERY

Approximately 2% of the geriatric population, including 3% of women 75 years of age or older, will develop primary hyperparathyroidism.⁴⁷ Geriatric patients are usually referred to surgery only when advanced disease is present because of concerns regarding the risks of surgery, but low rates of morbidity and negligible mortality combined with high cure rates of approximately 95% to 98% make parathyroidectomy safe and effective. Convincing evidence of the benefit of surgery is the usual marked symptomatic improvement, which greatly improves the quality of life for most patients. The National Institutes of Health Consensus Development Statement recommends curative therapy after diagnosis of primary hyperthyroidism is established in a patient regardless of age. Specific indications for operative intervention regardless of age include a 30% decrease in creatinine clearance, 24-hour urinary calcium excretion >400 mg, and decreased bone density.⁴⁸

Elderly patients are especially prone to developing mental manifestations of hyperparathyroidism that may be severe enough to produce a dementia-like state. There often is a significant improvement in mental status after parathyroidectomy. Another specific symptom of hyperparathyroidism that may easily be mistaken for osteoporosis and can be present in postmenopausal, elderly women is orthopedic disease; specifically back pain, and possibly, the occurrence of vertebral fractures. This pain can be of moderate intensity, leading to impaired mobility and severely affecting the quality of life of elderly patients. The decreased bone density observed in elderly patients with hyperparathyroidism tends to improve during the first 2 years after successful parathyroid surgery.

Limited parathyroidectomies with minimal dissection in geriatric patients are an effective alternative. This is a viable option in patients with multiple comorbid conditions in whom the increased risk of surgical intervention or general anesthesia remains a concern. One study demonstrated that preoperative

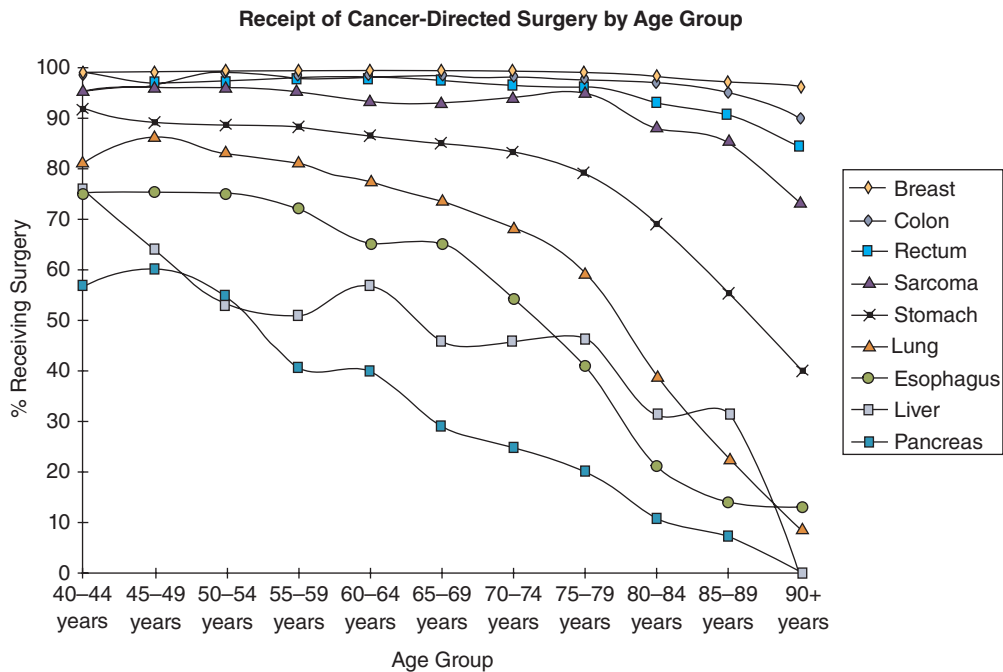


Figure 47-7. Decreased referrals of patients to oncologic surgery based on age. This graph includes potentially resectable lesions. The authors found that only 10% of patients over the age of 70 who had liver or pancreatic cancers were referred for cancer-directed surgery. (Reproduced with permission from O'Connell JB, Maggard MA, Ko CY. Cancer-directed surgery for localized disease: decreased use in the elderly. *Ann Surg Oncol*. 2004;11:962. With kind permission from Springer Science + Business Media.)

localization of the hyperfunctioning gland with the aid of ^{99m}Tc -sestamibi nuclear scanning, as well as intraoperative parathyroid hormone (PTH) assays to rapidly confirm that all hypersecreting glands have been removed, allows limited parathyroidectomy to be performed with accuracy in elderly patients.⁴⁷ This procedure is described as “limited” because bilateral neck dissection for identification and biopsy of the remaining glands to determine if they are hypersecreting becomes unnecessary. The half-life of intact PTH is approximately 3 to 4 minutes. Therefore, a drop in the intraoperative PTH level at approximately 10 minutes after resection of the suspect hypersecreting gland suggests a 98% probability that the patient will return to normocalcemic levels postoperatively.⁴⁷

PALLIATIVE SURGERY

Palliative surgery is defined as surgical intervention targeted to alleviate a patient's symptoms, thus improving the patient's quality of life despite minimal impact on the patient's survival.⁵⁴ With an increasing number of aging surgical patients who often present with advanced disease, surgeons must be familiar with the concept of palliation to control disease. This concept focuses on providing the maximal benefit to the patient using the least-invasive intervention. Ultimately, this leads to symptom relief and preservation of the quality of life in terminal disease states. The uses of palliative surgery can range from extensive debulking operations aimed at aiding in the effectiveness of chemotherapy and radiation, to less complex operations to alleviate symptoms such as intractable vomiting, severe pain, cachexia, and anorexia that are common to terminal disease states. The success of palliative surgery is a careful balance between achieving symptom relief while ensuring that the development of new symptoms from the palliative intervention itself does not occur.

THE ROLE OF THE SURGEON IN GERIATRIC PATIENTS IS NOT LIMITED TO THE OR

The need for surgical input in helping elderly patients make decisions has never been more important. Inherent biases to age exist, such that patients who can be cured or palliated by surgical procedures are in many cases not being helped. For example, O'Connell demonstrated a decrease in referrals to surgery in aged patients with potentially curable oncologic illnesses, including those of breast, gastrointestinal, and lung (Fig. 47-7).⁵⁰ Only a surgeon with knowledge of the current best practice approach for the aged patient can help a patient—and his or her referring physicians—understand the real risks and potential benefits of an intervention, be it curative or palliative.

The challenge for us is to improve perioperative care of the elderly surgical patient using new tools for careful patient selection, accurately assess risk factors to reduce postoperative morbidity and mortality, and deliver quality surgical interventions without compromising functional vitality.

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48 chapter

Ethics, Palliative Care, and Care at the End of Life

Daniel E. Hall, Peter Angelos, Geoffrey P. Dunn,
Daniel B. Hinshaw, and Timothy M. Pawlik

Why Ethics Matter	1941	General Principles of Palliative Care / 1946	Pronouncing Death / 1949
Definitions and Overview	1941	Concepts of Suffering, Pain, Health, and Healing / 1947	Professional Ethics: Conflict of Interest, Research, and Clinical Ethics
Specific Issues in Surgical Ethics	1942	Effective Communication and Negotiating the Goals of Care / 1947	1949
Informed Consent / 1942		Care at the End of Life	Conflict of Interest / 1949
The Boundaries of Autonomy: Advanced Directives and Powers of Attorney / 1944		1948	Research Ethics / 1952
Withdrawing and Withholding Life-Sustaining Therapies / 1945		The Syndrome of Imminent Demise / 1948	Special Concerns in Surgical Research / 1952
Palliative Care	1946	Common Symptoms at the End of Life and Their Management / 1948	Surgical Innovation and Surgical Research / 1952
			Clinical Ethics: Disclosure of Errors / 1952

Dedicated to the advancement of surgery along its scientific and moral side.

June 10, 1926, dedication on the Murphy Auditorium, the first home of the American College of Surgeons

WHY ETHICS MATTER

Ethical concerns involve not only the interests of patients, but also the interests of surgeons and society. Surgeons choose among the options available to them because they have particular opinions regarding what would be good (or bad) for their patients. Aristotle described practical wisdom (Greek: *phronesis*) as the capacity to choose the best option from among several imperfect alternatives (Fig. 48-1).¹ Frequently, surgeons are confronted with clinical or interpersonal situations in which there is incomplete information, uncertain outcomes, and/or complex personal and familial relationships. The capacity to choose wisely in such circumstances is the challenge of surgical practice.

DEFINITIONS AND OVERVIEW

Biomedical ethics is the system of analysis and deliberation dedicated to guiding surgeons toward the “good” in the practice of surgery. One of the most influential ethical “systems” in the field of biomedical ethics is the principlist approach as articulated by Beauchamp and Childress.² In this approach to ethical issues, moral dilemmas are deliberated by using four guiding principles: autonomy, beneficence, nonmaleficence, and justice.²

The principle of autonomy respects the capacity of individuals to choose their own destiny, and it implies a right for individuals to make those choices. It also implies an obligation for physicians to permit patients to make autonomous choices about their medical care. Beneficence requires that proposed actions aim

at and achieve something good whereas nonmaleficence aims at avoiding concrete harm: *primum non nocere*®. Justice requires fairness where both the benefits and burdens of a particular action are distributed equitably.

The history of medical ethics has its origins in antiquity. The Hippocratic Oath along with other professional codes has guided the actions of physicians for thousands of years. However, the growing technical powers of modern medicine raise new questions that were inconceivable in previous generations. Life support, dialysis, and modern drugs, as well as organ and cellular transplantation, have engendered new moral and ethical questions. As such, the ethical challenges faced by the surgeon have become more complex and require greater attention.

The case-based paradigm for bioethics is used when the clinical team encounters a situation in which two or more values or principles come into apparent conflict. The first step is to clarify the relevant principles (e.g., autonomy, beneficence, nonmaleficence, and justice) and values at stake (e.g., self-determination, quality of life, etc.). After identifying the principles and values that are affecting the situation, a proposed course of action is considered given the circumstances.

Much of the discourse in bioethics adopts this “principlist” approach in which the relevant principles are identified, weighed and balanced, and then applied to formulate a course of action. This approach to bioethics is a powerful technique for thinking through moral problems because the four principles help identify what is at stake in any proposed course of action. However, the principles themselves do not resolve ethical dilemmas. Working together, patients and surgeons must use wise judgment to choose the best course of action for the specific case.

Choosing wisely requires the virtue of practical wisdom first described by Aristotle (Fig. 48-1). Along with the other cardinal virtues of courage, justice and temperance, practical wisdom is a central component of virtue ethics which complement principlist

*“First do no harm.”

Key Points

- 1▶ The physician should document that the patient or surrogate has the capacity to make a medical decision.
- 2▶ The physician discloses to the patient details regarding the diagnosis and treatment options sufficient for the patient to make an informed consent.
- 3▶ Living wills are written to anticipate treatment options and choices in the event that a patient is rendered incompetent by a terminal illness.
- 4▶ The durable power of attorney for healthcare identifies surrogate decision makers and invests them with the authority to make healthcare decisions on the patient's behalf in the event that they are unable to speak for themselves.
- 5▶ Surgeons should encourage their patients to clearly identify their surrogates early in the course of treatment.
- 6▶ Earlier referral and wider use of palliative and hospice care may help more patients achieve their goals at the end of life.
- 7▶ Seven requirements for the ethical conduct of clinical trials have been articulated: value, scientific validity, fair subject selection, favorable risk-benefit ratio, independent review, informed consent, and respect for enrolled subjects.
- 8▶ Disclosure of error is consistent with recent ethical advances in medicine toward more openness with patients and the involvement of patients in their care.

ethics by guiding choices toward the best options for treatment. Practical wisdom cannot be learned from books and is developed only through experience. The apprenticeship model of surgical residency fosters the development of practical wisdom through experience. More than teaching merely technical mastery, surgical residency is also moral training. In fact, the sociologist Charles Bosk argues that the “postgraduate training of surgeons is above all things an ethical training.”³

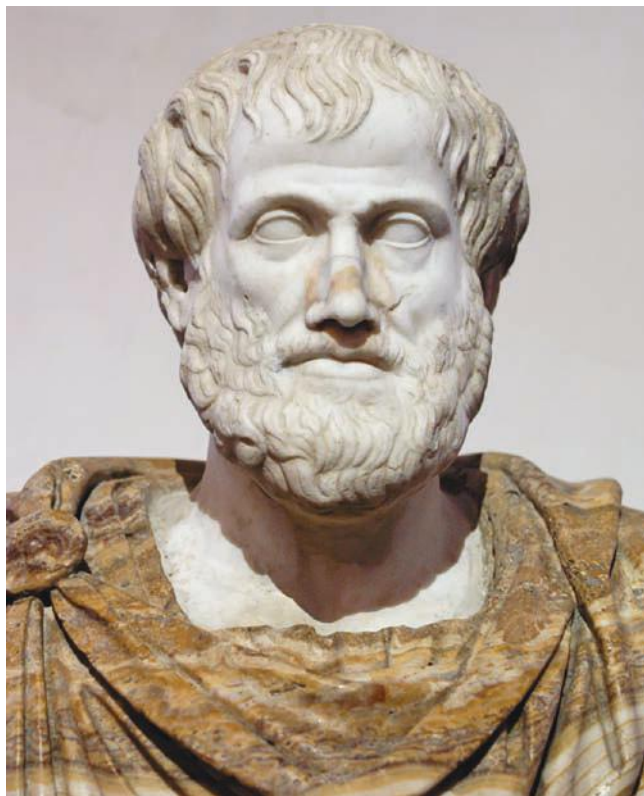


Figure 48-1. Bust of Aristotle. Marble, Roman copy after a Greek bronze original by Lysippos from 330 B.C. [From http://en.wikipedia.org/wiki/File:Aristotle_Altemps_Inv8575.jpg: Ludovisi Collection, Accession number Inv. 8575, Palazzo Altemps, Location Ground Floor, Branch of the National Roman Museum. Photographer/source Jastrow (2006) from Wikipedia (accessed April 8, 2014).]

SPECIFIC ISSUES IN SURGICAL ETHICS

Informed Consent

Although a relatively recent development, the doctrine of informed consent is one of the most widely established tenets of modern biomedical ethics. During the nineteenth and early twentieth centuries, most physicians practiced a form of benign paternalism whereby patients were rarely involved in the decision-making process regarding their medical care, relying instead on the beneficence of the physician. Consensus among the wider public eventually changed such that surgeons are now expected to have an open discussion about diagnosis and treatment with the patient to obtain informed consent. In the United States, the legal doctrine of *simple* consent dates from the 1914 decision in *Schloendorff vs. The Society of New York Hospital* regarding a case in which a surgeon removed a diseased uterus after the patient had consented to an examination under anesthesia, but with the express stipulation that no operative excision should be performed. The physician argued that his decision was justified by the beneficent obligation to avoid the risks of a second anesthetic. However, Justice Benjamin Cardozo stated:

*Every human being of adult years and sound mind has a right to determine what shall be done with his body; and a surgeon who performs an operation without his patient's consent commits an assault, for which he is liable in damages . . . except in cases of emergency, where the patient is unconscious, and where it is necessary to operate before consent can be obtained.*⁴

Having established that patients have the right to determine what happens to their bodies, it took some time for the modern concept of *informed* consent to emerge from the initial doctrine of *simple* consent. The initial approach appealed to a *professional practice standard* whereby physicians were obligated to disclose to patients the kind of information that experienced surgeons customarily disclosed.⁵ However, this disclosure was not always adequate for patient needs. In the 1972 landmark case, *Canterbury vs. Spence*, the court rejected the professional practice standard in favor of the *reasonable person standard* whereby physicians are obliged to disclose to patients all information regarding diagnosis, treatment options, and risks that a “reasonable patient” would want to know in a similar situation. Rather than relying on the practices or consensus of the medical community, the reasonable person standard empowers

the public (reasonable persons) to determine how much information should be disclosed by physicians to ensure that consent is truly informed. The court did recognize, however, that there are practical limits on the amount of information that can be communicated or assimilated.⁵ Subsequent litigation has revolved around what reasonable people expect to be disclosed in the consent process to include the nature and frequency of potential complications, the prognostic life expectancy,⁶ and the surgeon-specific success rates.⁴ Despite the litigious environment of medical practice, it is difficult to prosecute a case of inadequate informed consent so long as the clinician has made a concerted and documented effort to involve the patient in the decision-making process.

Adequate informed consent entails at least four basic elements: (a) the physician documents that the patient or surrogate has the capacity to make a medical decision; (b) **1▶** the surgeon discloses to the patient details regarding the diagnosis and treatment options sufficiently for the patient to make an informed choice; (c) the patient demonstrates understanding of the disclosed information before (d) **2▶** authorizing freely a specific treatment plan without undue influence (Fig. 48-2). These goals are aimed at respecting each patient's prerogative for autonomous self-determination. To accomplish these goals, the surgeon needs to engage in a discussion about the causes and nature of the patient's disease, the risks and benefits of available treatment options, as well as details regarding what patients can expect after an operative intervention.⁷⁻¹⁴

Informed consent can be challenging in certain clinical settings. For example, obtaining consent for emergency surgery, where decisions are often made with incomplete information,

can be difficult. Emergency consent requires the surgeon to consider if and how possible interventions might save a patient's life, and if successful, what kind of disability might be anticipated. Surgical emergencies are one of the few instances where the limits of patient autonomy are freely acknowledged, and surgeons are empowered by law and ethics to act promptly in the best interests of their patients according to the surgeon's judgment. Most applicable medical laws require physicians to provide the standard of care to incapacitated patients, even if it entails invasive procedures without the explicit consent of the patient or surrogate. If at all possible, surgeons should seek the permission of their patients to provide treatment, but when emergency medical conditions render patients unable to grant that permission, and when delay is likely to have grave consequences, surgeons are legally and ethically justified in providing whatever surgical treatment the surgeon judges necessary to preserve life and restore health.⁴ This justification is based on the social consensus that most people would want their lives and health protected in this way, and this consensus is manifest in the medical profession's general orientation to preserve life. It may be that subsequent care may be withdrawn or withheld when the clinical prognosis is clearer, but in the context of initial resuscitation of injured patients, incomplete information makes clear judgments about the patient's ultimate prognosis or outcome impossible.

The process of consent can also be challenging in the pediatric population. For many reasons, children and adolescents cannot participate in the process of giving informed consent in the same way as adults. Depending on their age, children may lack the cognitive and emotional maturity to participate fully

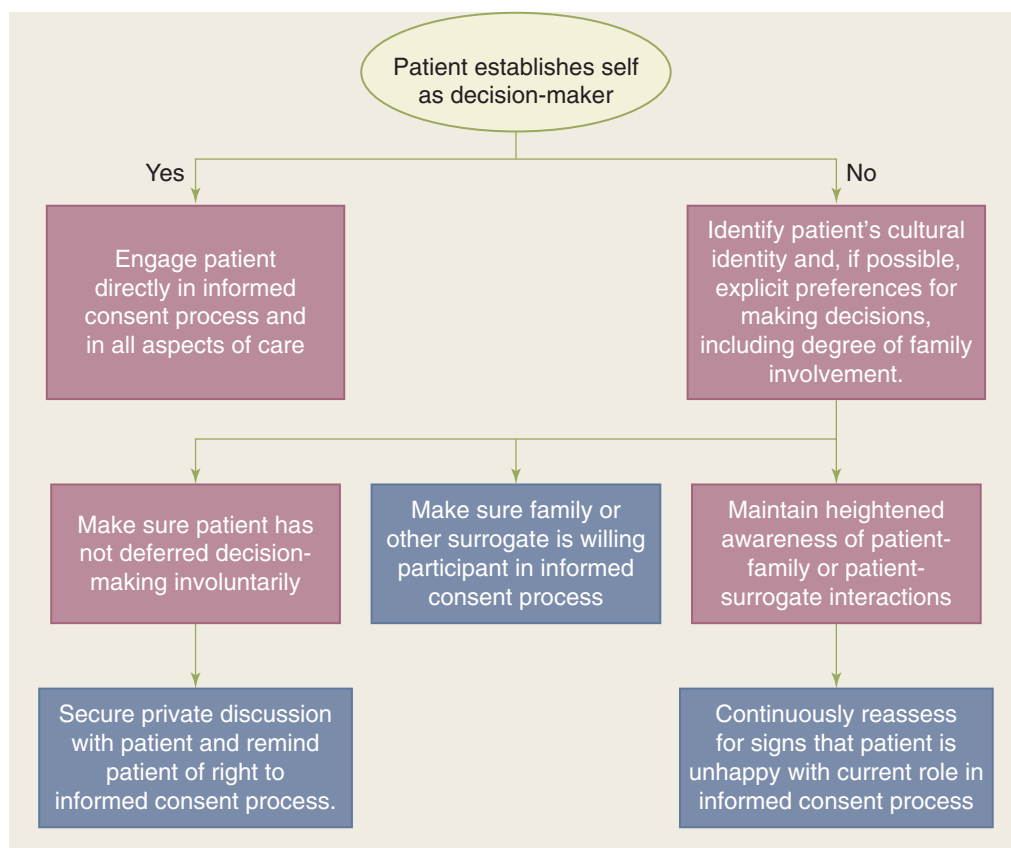


Figure 48-2. Algorithm for navigating the process of informed consent. (From Childers R, Lipsett A, Pawlik T. *Informed consent and the surgeon*. *J Am Coll Surg*. E-pub Jan. 21, 2009. Copyright 2009, with permission from Elsevier.)

in the process. In addition, depending on the child's age, their specific circumstances, as well as the local jurisdiction, children may not have legal standing to fully participate on their own independent of their parents. The use of parents or guardians as surrogate decision makers only partially addresses the ethical responsibility of the surgeon to involve the child in the informed consent process. The surgeon should strive to augment the role of the decision makers by involving the child in the process. Specifically, children should receive age-appropriate information about their clinical situation and therapeutic options so that the surgeon can solicit the child's "assent" for treatment. In this manner, while the parents or surrogate decision makers formally give the informed consent, the child remains an integral part of the process.

Certain religious practices can present difficulties in treating minor children in need of life-saving blood transfusions; however, case law has made clear the precedent that parents, regardless of their held beliefs, may not place their minor children at mortal risk. In such a circumstance, the physician should seek counsel from the hospital medicolegal team, as well as from the institutional ethics team. Legal precedent has, in general, established that the hospital or physician can proceed with providing all necessary care for the child.

Obtaining "consent" for organ donation deserves specific mention.¹⁵ Historically, discussion of organ donation with families of potential donors was performed by transplant professionals, who were introduced to families by intensivists after brain death had been confirmed and the family had been informed of the fact of death. In other instances, consent might be obtained by intensivists caring for the donor, as they were assumed to know the patient's family and could facilitate the process. However, issues of moral "neutrality" as part of end-of-life care in the intensive care unit have caused a shift in how obtaining "consent" for organ donation is handled. Responsibility for obtaining consent from the donor family is now vested in trained "designated requestors" (or "organ procurement coordinators")¹⁶ or by "independent" intensivists who do not have a therapeutic clinical relationship with the potential donor.¹⁷ In this way, the donor family can be allowed to make the decision regarding donation in a "neutral" environment without erosion of the therapeutic relationship with the treating physician.

The process of informed consent also can be limited by the capacity of patients to assimilate information in the context of their illness. For example, despite the best efforts of surgeons, evidence suggests that patients rarely retain much of what is disclosed in the consent conversation, and they may not remember discussing details of the procedure that become relevant when postoperative complications arise.¹⁸ It is important to recognize that the doctrine of informed consent places the most emphasis on the principle of autonomy precisely in those clinical situations when, because of their severe illness or impending death, patients are often divested of their autonomy.

The Boundaries of Autonomy: Advanced Directives and Powers of Attorney

Severe illness and impending death can often render patients incapable of exercising their autonomy regarding medical decisions. One approach to these difficult situations is to make decisions in the "best interests" of patients, but because such decisions require value judgments about which thoughtful people frequently disagree, ethicists, lawyers, and legislators have sought a more reliable solution. Advanced directives of

various forms have been developed to carry forward into the future the autonomous choices of competent adults regarding health care decisions. Furthermore, the courts often accept "informal" advanced directives in the form of sworn testimony about statements the patient made at some time previous to their illness. When a formal document expressing the patient's advanced directives fails to exist, surgeons should consider the comments patients and families make when asked about their wishes in the setting of debilitating illness.

Living wills are written to anticipate treatment options and choices in the event that a patient is incapacitated by a terminal illness. In the living will, the patient indicates which treatments she wishes to permit or prohibit in the setting of terminal illness. The possible treatments addressed often include mechanical ventilation, cardiopulmonary resuscitation, artificial nutrition, dialysis, antibiotics, or transfusion of blood products. Unfortunately, living wills are often too vague to offer concrete guidance in complex clinical situations, and the language ("terminal illness," "artificial nutrition") can be interpreted in many ways. Furthermore, by limiting the directive only to "terminal" conditions, it does not provide guidance for common clinical scenarios like advanced dementia, delirium, or persistent vegetative states where the patient is unable to make decisions, but is not "terminally" ill. Perhaps even more problematic is the evidence that demonstrates that healthy patients cannot reliably predict their preferences when they are actually sick. This phenomenon is called "affective forecasting" and applies to many situations. For example, the general public estimates the health-related quality of life (HRQoL) score of patients on dialysis at 0.39, although dialysis patients themselves rate their HRQoL at 0.56.¹⁹ Similarly, patients with colostomies rated their HRQoL at 0.92, compared to a score of 0.80 given by the general public for patients with colostomies.¹⁹ For these and other reasons, living wills are often unable to provide the extent of assistance they promise.²⁰

An alternative to living wills is the durable power of attorney for health care in which patients identify surrogate decision makers and invest them with the authority to make health care decisions on their behalf in the event that they are unable to speak for themselves. Proponents of this approach hope that the surrogate will be able to make decisions that reflect the choices that the patients themselves would make if they were able. Unfortunately, several studies demonstrate that surrogates are not much better than chance at predicting the choices patients make when the patient is able to state a preference. For example, a recent meta-analysis found that surrogates predicted patients' treatment preferences with only 68% accuracy.²¹ These data reveal a flaw in the guiding principle of surrogate decision making: Surrogates do not necessarily have privileged insight into the autonomous preferences of patients. However, the durable power of attorney at least allows patients to choose the person who will eventually make prudential decisions on their behalf and in their best interests; therefore, respecting the judgment of the surrogate is a way of respecting the self-determination of the incapacitated patient.²²

There is continuing enthusiasm for a wider use of advanced directives. In fact, the 1991 Patient Self Determination Act requires all U.S. health care facilities to (a) inform patients of their rights to have advanced directives, and (b) to document those advanced directives in the chart at the time any patient is admitted to the health care facility.⁴ However, only a minority of patients in U.S. hospitals have advanced directives despite

concerted efforts to teach the public of their benefits. For example, the ambitious SUPPORT trial used specially trained nurses to promote communication between physicians, patients, and their surrogates to improve the care and decision making of critically ill patients. Despite this concerted effort, the intervention demonstrated “no significant change in the timing of do not resuscitate (DNR) orders, in physician-patient agreement about DNR orders, in the number of undesirable days (patients experiences), in the prevalence of pain, or in the resources consumed.”²³

Some of the reluctance around physician-patient agreement about DNR orders may reflect patient and family anxiety that DNR orders equate to “do not treat.” Patients and families should be assured, when appropriate, that declarations of DNR/do not intubate will not necessarily result in a change in ongoing routine clinical care. The issue of temporarily rescinding DNR/do not intubate orders around the time of an operative procedure may also need to be addressed with the family.

Patients should be encouraged to clearly identify their surrogates, both formally and informally, early in the course of treatment, and before any major elective operation. Often, **5▶** around the time of surgery or at the end of life, there are limits to patient autonomy in medical decision making. Seeking an advanced directive or surrogate decision maker requires time that is not always available when the clinical situation deteriorates. As such, these issues should be clarified as early as possible in the patient-physician relationship.

Withdrawing and Withholding Life-Sustaining Therapies

The implementation of various forms of life support technology raise a number of legal and ethical concerns about when it is permissible to withdraw or withhold available therapeutic technology. There is general consensus among ethicists that there are no philosophic differences between withdrawing (stopping) or withholding (not starting) treatments that are no longer beneficial.²⁴ However, the right to refuse, withdraw, and withhold beneficial treatments was not established before the landmark case of Karen Ann Quinlan. In 1975, Quinlan lapsed into a persistent vegetative state requiring ventilator support. After several months without clinical improvement, Quinlan’s parents asked the hospital to withdraw ventilator support. The hospital refused, fearing prosecution for euthanasia. The case was appealed to the New Jersey Supreme Court where the justices ruled that it was permissible to withdraw ventilator support.²⁵ This case established a now commonly recognized right to withdraw “extraordinary” life-saving technology if it is no longer desired by the patient or the patient’s surrogate.

The difference between “ordinary” and “extraordinary” care, and whether there is an ethical difference in withholding or withdrawing “ordinary” vs. “extraordinary” care, has been an area of much contention. The 1983 Nancy Cruzan case highlighted this issue. In this case, Cruzan had suffered severe injuries in an automobile crash that rendered her in a persistent vegetative state. Cruzan’s family asked that her tube feeds be withheld, but the hospital refused. The case was appealed to the U.S. Supreme Court, which ruled that the tube feeding could be withheld if her parents demonstrated “clear and convincing evidence” that the incapacitated patient would have rejected the treatment.²⁶ In this ruling, the court essentially ruled that there was no legal distinction between “ordinary” vs. “extraordinary” life-sustaining therapies.²⁷ In allowing the feeding tube to be

removed, the court accepted the principle that a competent person (even through a surrogate decision maker) has the right to decline treatment under the Fourteenth Amendment of the U.S. Constitution. The court noted, however, that there has to be clear and convincing evidence of the patient’s wishes (principle of autonomy) and that the burdens of the medical intervention should outweigh its benefits (consistent with the principles of beneficence and nonmaleficence).

In deliberating the issue of withdrawing vs. withholding life-sustaining therapies, the principle of “double effect” is often mentioned. According to the principle of “double effect,” a treatment (e.g., opioid administration in the terminally ill) that is intended to help and not harm the patient (i.e., relieve pain) is ethically acceptable even if an unintended consequence (side effect) of its administration is to shorten the life of the patient (e.g., by respiratory depression). Under the principle of double effect, a physician may withhold or withdraw a life-sustaining therapy if the surgeon’s *intent* is to relieve suffering, not to hasten death. The classic formulation of double effect has four elements (Fig. 48-3).

Withholding or withdrawing of life-sustaining therapy is ethically justified under the principle of double effect if the physician’s intent is to relieve suffering, not to kill the patient. Thus, in managing the distress of the dying, there is a fundamental ethical difference between titrating medications rapidly to achieve relief of distress and administering a very large bolus with the intent of causing apnea. It is important to note, however, that although the use of opioids for pain relief in advanced illness is frequently cited as the classic example of the double effect rule, opioids can be used safely without significant risk. In fact, if administered appropriately, in the vast majority of instances the

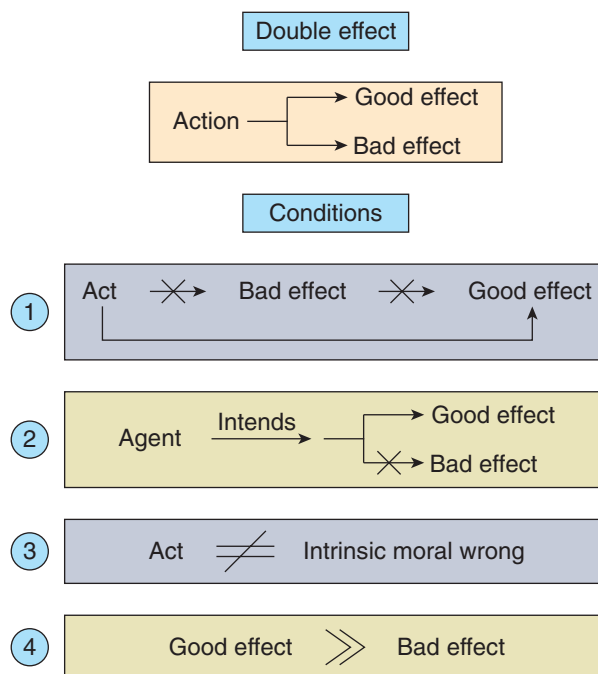


Figure 48-3. The four elements of the double effect principle: a) The good effect is produced directly by the action and not by the bad effect. b) The person must intend only the good effect, even though the bad effect may be foreseen. c) The act itself must not be intrinsically wrong, or needs to be at least neutral. d) The good effect is sufficiently desirable to compensate for allowing the bad effect.

rule of double effect need not be invoked when administering opioids for symptom relief in advanced illness.²⁸

In accepting the ethical equivalence of withholding and withdrawing of life-sustaining therapy, surgeons can make difficult treatment decisions in the face of prognostic uncertainty.²⁴ In light of this, some important principles to consider when considering withdrawal of life-sustaining therapy include: (a) Any and all treatments can be withdrawn. If circumstances justify withdrawal of one therapy (e.g., IV pressors, antibiotics), they may also justify withdrawal of others; (b) Be aware of the symbolic value of continuing some therapies (e.g., nutrition, hydration) even though their role in palliation is questionable; (c) Before withdrawing life-sustaining therapy, ask the patient and family if a spiritual advisor (e.g., pastor, imam, rabbi, or priest) should be called; and (d) Consider requesting an ethics consult.

Although the clinical setting may seem limited, a range of options usually exists with respect to withdrawing or withholding treatment, allowing for an incremental approach, for example (a) continuing the current regimen without adding new interventions or tests; (b) continuing the current regimen but withdrawing elements when they are no longer beneficial; and (c) withdrawing and withholding all treatments that are not targeted to relieve symptoms and maximize patient comfort.²⁹

The surgeon might consider discussing the clinical situation with the patient or proxy decision maker, identify the various therapeutic options, and delineate the reasons why withholding or withdrawing life-sustaining therapy would be in the patient's best interest. If the patient (or designated proxy decision maker) does not agree with withholding or withdrawing life-sustaining therapy, the surgeon should consider or recommend a second medical opinion. If the second opinion corroborates that life-sustaining therapy should be withheld or withdrawn but the patient/family continues to disagree, the surgeon should consider assistance from institutional resources such as the ethics committee and hospital administration. Although the surgeon is not ethically obligated to provide treatment that he or she believes is futile, the surgeon is responsible for continued care of the patient, which may involve transferring the patient to a surgeon who is willing to provide the requested intervention.²⁴

PALLIATIVE CARE

General Principles of Palliative Care

Palliative care is a coordinated, interdisciplinary effort that aims to relieve suffering and improve quality of life for patients and their families in the context of serious illness.³⁴ It is offered simultaneously with all other appropriate medical treatment, and its indication is not limited to situations associated with a poor prognosis for survival. Palliative care strives to achieve more than symptom control, but it should not be confused with noncurative treatment.

The World Health Organization defines palliative care as “an approach that improves the quality of life of patients and their families facing the problems associated with life-threatening illness, through the prevention and relief of suffering by means of early identification and impeccable assessment and treatment of pain and other problems, physical, psychosocial, and spiritual.”²⁹ Palliative care is both a philosophy of care and an organized, highly structured system for delivering care.

Palliative care includes the entire spectrum of intervention for the relief of symptoms and the promotion of quality of life.

No specific therapy, including surgical intervention, is excluded from consideration. Therefore, surgeons have valuable contributions to make to palliative care. In fact, the term *palliative care* was coined in 1975 by Canadian surgeon, Balfour Mount. Furthermore, *surgical palliative care* can be defined as the treatment of suffering and the promotion of quality of life for seriously or terminally ill patients under the care of surgeons.³¹ The standard of palliative treatment lies in the agreement between patient and physician that the expected outcome is relief from distressing symptoms, lessening of pain, and improvement of quality of life. The decision to intervene is based on the treatment's ability to meet the stated goals, rather than its impact on the underlying disease.

The fundamental elements of palliative care consist of pain and nonpain symptom management, communication among patients, their families, and care providers, and continuity of care across health systems and through the trajectory of illness. Additional features of system-based palliative care are team-based planning that includes patient and family; close attention to spiritual matters; and psychosocial support for patients, their families, and care providers, including bereavement support.

Indications for palliative care consultation in surgical practice include: (a) patients with conditions that are progressive and life-limiting, especially if characterized by burdensome symptoms, functional decline, and progressive cognitive deficits; (b) assistance in clarification or reorientation of patient/family goals of care; (c) assistance in resolution of ethical dilemmas; (d) situations in which a patient/surrogate declines further invasive or curative treatments with stated preference for comfort measures only; (e) patients who are expected to die imminently or shortly after hospital discharge; and (f) provision of bereavement support for patient care staff, particularly after loss of a colleague under care³¹ (Table 48-1). Although all patients, regardless of prognosis, may benefit from the services of a palliative care physician, hospice care is a specific form of palliative care intended for patients who have an estimated prognosis of 6 months or less to live. Hospice care is covered under Medicare Part A, and benefits may be continued beyond the original 6 months of estimated survival if physicians certify that life expectancy remains limited to 6 months or less.

▶ Although most Americans indicate a preference to die at home, nearly 75% die in an institutional setting. Earlier referral and wider use of the hospice benefit may help more patients achieve their goal of dying at home.

Table 48-1

Indications for palliative care consultation

Patients with conditions that are progressive and life-limiting, especially if characterized by burdensome symptoms, functional decline, and progressive cognitive deficits
Assistance in clarification or reorientation of patient/family goals of care
Assistance in resolution of ethical dilemmas
Situations in which patient/surrogate declines further invasive or curative treatments with stated preference for comfort measures only
Patients who are expected to die imminently or shortly after hospital discharge
Provision of bereavement support for patient care staff, particularly after loss of a colleague under care

Concepts of Suffering, Pain, Health, and Healing

Palliative care addresses specifically the individual patient's experience of suffering due to illness. Indeed, the philosophical origins of palliative care began with attention to suffering and the existential questions suffering engenders. More than mere technologic evolution in the management of symptoms, the early proponents of palliative care sought a revolution in the moral foundations of medicine that challenged the assumptions that so often seemed to result in futile invasive intervention, and identified many of the problems that were subsequently taken up by medical ethicists. This reorientation of the goals of medical care from a focus on disease and its management to the patient's experience of illness focuses attention on the purpose of medicine and the meaning of health and healing.

Over the past half century, several concepts and theories about the nature of pain, suffering, and health have been proposed in service of the evolving conceptual framework of palliative care. For example, while considering the differences between disease-oriented and illness-oriented approaches to the care of seriously ill patients, psychiatrist Arthur Kleinman wrote, "There is a moral core to healing in all societies. [Healing] is the central purpose of medicine . . . the purpose of medicine is both control of disease processes and care for the illness experience. Nowhere is this clearer than in the relationship of the chronically ill to their medical system: For them, the control of disease is by definition limited; care for the life problems created by the disorder is the chief issue."³⁴

The relief of pain has been the clinical foundation for hospice and palliative care. It has been defined by the International Association for the Study of Pain as "An unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage."³⁵ For purposes of interdisciplinary palliative care, Saunders's concept of "Total Pain"³¹ is a more useful definition and is frequently used as the basis for palliative assessments. Total Pain is the sum total of four principal domains of pain: physical, psychologic, social or socioeconomic, and spiritual. Each of these contributes to, but is not synonymous with, suffering.

Effective Communication and Negotiating the Goals of Care

Changing the goals of care from cure to palliation near the end of life is both emotionally and clinically challenging, and it depends on a clear prognosis and effective communication. Unfortunately, prognostication can be notoriously difficult and inaccurate in advanced illness, and Christakis has argued that, to a large degree, physicians have abdicated their traditional responsibility to provide clear prognosis regarding incurable disease and approaching death.³⁷ However, there are validated tools for prognosis in critical illness (APACHE, MODS, etc.), and with most advanced diseases, functional status is the most powerful predictor of survival. For example, patients with advanced metastatic cancer who are resting/sleeping for 50% or more of normal waking hours and require some assistance with activities of daily living (ADL) have a projected survival of weeks, and patients who are essentially bedfast and dependent for ADL have a projected survival of days to a week or two at best. Table 48-2 shows a simple prognostic tool to aid clinicians in recognizing patients nearing the end of life.

Alternatively, the Karnofsky Performance Scale is a scale of functional status ranging from 100 (high level of function) to

Table 48-2

Simple prognostication tool in advanced illness (especially cancer)

FUNCTIONAL LEVEL	PERFORMANCE STATUS (ECOG)	PROGNOSIS
Able to perform all basic ADLs independently and some IADLs	2	Months
Resting/sleeping up to 50% or more of waking hours and requiring some assistance with basic ADLs	3	Weeks to a few months
Dependent for basic ADLs and bed-to-chair existence	4	Days to a few weeks at most

These observations apply to patients with advanced, progressive, incurable illnesses (e.g., metastatic cancer refractory to treatment). Basic ADL = activities of daily living (e.g., transferring, toileting, bathing, dressing, and feeding oneself); IADL = instrumental activities of daily living (e.g., more complex activities such as meal preparation, performing household chores, balancing a checkbook, shopping, etc.); ECOG = Eastern Cooperative Oncology Group functional (performance) status.

0 (death). It is commonly used in palliative care to roughly assess patient anticipated needs as well as prognosis. The Palliative Performance Scale³⁸ is a validated³⁹ expansion of the Karnofsky Performance Scale that includes five palliative-focused domains, including ambulation, activity level, self-care, intake, and level of consciousness, in addition to evidence of disease. The Missoula-Vitas Quality of Life Index is a 25-question scale specifically for palliative care and hospice patients that scores symptoms, function, interpersonal relationships, well-being, and spirituality. Updates and Spanish versions are available.³⁶

Regardless of the prognostic tool used, the prognosis should be conveyed to the patient and family. If done well, communication and negotiation with patients and families about advanced terminal illnesses can potentially avoid great psychologic harm and help make a difficult transition easier. To communicate effectively and compassionately, it is helpful to pursue an organized process similar to the structured history and physical central to the evaluation of any patient. One such structured approach to delivering unfavorable news proposes six steps that can be easily learned by clinicians: (a) getting started by selection of the appropriate setting, introductions, and seating; (b) determining what the patient or family knows; (c) determining what the patient or family wants to know; (d) giving the information; (e) expressing empathy; and (f) establishing expectations, planning, and aftercare (Table 48-3).⁴⁰ Success with this approach to breaking bad news is critically dependent upon the clinician's ability to empathically respond to the patient's (and family's) reaction to the news.⁴¹ The empathic response does not require the surgeon to share the same emotions of the patient, but it does require the surgeon to identify the patient's emotion and accurately reflect that awareness back to the patient. Patient assessment in these conversations should give the highest priority to identifying and responding to the most immediate source of distress. Relieving a pressing symptom is prerequisite for a more thorough search for other potential sources of

Table 48-3

Communicating unfavorable news: Important principles

- Setting: Find a quiet, private place to meet. Sit down close to the patient.
- Listen: Clarify the patient's and/or the family's understanding of the situation.
- "Warning shot": Prepare patient and family and obtain their permission to communicate bad news (e.g., "I'm afraid I have bad news.>").
- Silence: Pause after giving bad news. Allow patient/family to absorb/react to the news.
- Encourage: Convey hope that is realistic and appropriate to the circumstances (e.g., patient will not be abandoned; symptoms will be controlled).

suffering, and the assessment process, itself, can be therapeutic if conducted in a respectful and gentle manner.

CARE AT THE END OF LIFE

The process of dying and the care of a patient at the time of death is a distinct clinical entity that demands specific skills from physicians. The issues specific to dying and the available tools for compassionate care at the end of life are addressed in this section.

The Syndrome of Imminent Demise^{29,42}

In a patient who has progressed to the terminal stage of an advanced illness (e.g., cancer), a number of signs provide evidence of imminent death. As terminally ill patients progress toward death, they become increasingly bedbound, requiring assistance for all basic ADL. There is a steady decrease in desire and requests for food and fluids. More distressing to the dying patient is a progressively dry mouth that may be confused by the treating team as thirst. It is often exacerbated by anticholinergic medications, mouth breathing, and supplemental oxygen (O₂) administered without humidification.

With progressive debility, fatigue, and weight loss, it is common for terminally ill patients to experience increasing difficulty swallowing. This may result in aspiration episodes and an inability to swallow tablets, requiring alternative routes for medication administration (e.g., IV, SC, PR, sublingual, buccal, or transdermal). In addition to the increased risk of aspiration, patients near death develop great difficulty clearing oropharyngeal and upper airway secretions, leading to noisy breathing or the so-called "death rattle." As death approaches, the respiratory pattern may change to increasingly frequent periods of apnea often following a Cheyne-Stokes pattern of rapid, progressively longer breaths leading up to an apneic period. As circulatory instability develops near death, patients may exhibit cool and mottled extremities. Periods of confusion are often accompanied by decreasing urine output and episodes of fecal and urinary incontinence.

A number of cognitive changes occur as death approaches. Patients who are in the last days of life may demonstrate some signs of confusion or delirium. Agitated delirium is a prominent feature of a difficult death. Other cognitive changes that may be seen include a decreased interest in social interactions, increased somnolence, reduced attention span, disorientation to time (often with altered sleep-wake cycles), and an altered

dream life, including vivid "waking dreams" or visual hallucinations. Reduced hearing and visual acuity may be an issue for some patients; however, patients who appear comatose may still be aware of their surroundings. Severely cachectic patients may lose the ability to keep their eyes closed during sleep because of loss of the retro-orbital fat pad.

Common Symptoms at the End of Life and Their Management^{29,42,43}

The three most common, major symptoms that threaten the comfort of dying patients in their last days are respiratory distress, pain, and cognitive failure. General principles that are applicable to symptom management in the last days of life include: (a) anticipating symptoms before they develop; (b) minimizing technologic interventions (usually manage symptoms with medications); and (c) planning alternative routes for medications in case the oral route fails. It may be possible to cautiously reduce the dose of opioids and other medications as renal clearance decreases near the end of life, but it is important to remember that increased somnolence and decreasing respirations are prominent features of the dying process independent of medication side effects. Sudden cessation of opioid analgesics near the end of life could precipitate withdrawal symptoms, and therefore, medications should not be stopped for increasing somnolence or slowed respirations.

The principles of pharmacotherapy for pain and non-pain symptoms in the palliative care setting are outlined in Table 48-4. The World Health Organization,³⁰ the United States Agency for Health Care Policy and Research,⁴⁴ the Academy of Hospice and Palliative Medicine,⁴⁵ and many other agencies have endorsed a "step ladder" approach to cancer pain management that can predictably result in satisfactory pain control in most patients (Table 48-5). More refractory pain problems require additional expertise, and occasionally, more invasive approaches (Tables 48-6 and 48-7).

The primary treatment of dyspnea (air hunger) in the dying is opioids, which should be cautiously titrated to increase comfort and reduce tachypnea to a range of 15 to 20 breaths/min. Air movement across the face generated by a fan can sometimes be quite helpful. If this is not effective, empirical use of supplemental O₂ by nasal cannula (2–3 L/min) may bring some subjective relief, independent of observable changes in pulse oximetry. Supplemental O₂ should be humidified to avoid exacerbation of dry mouth. Typical starting doses of an immediate release opioid for breathlessness should be one-half to two-thirds of a starting dose of the same agent for cancer pain. For patients already on opioids for pain, a 25% to 50% increment in the dose of the current immediate release agent for breakthrough pain often will be effective in relieving breathlessness in addition to breakthrough pain.

The availability and variety of drugs should not prevent consideration of nonpharmacologic therapy. Massage therapy, music therapy, art therapy, guided imagery, hypnosis, physical therapy, pet therapy, and others play a constructive role not only for the relief of symptoms, but for promoting a sense of hope through improving function, aesthetic pleasure, and social connectedness. Talents and capacities neglected during the treatment and progression of disease can be recovered even in the most advanced stages of illness.

Pain is often less of a problem in the last days of life because the reduced activity level is associated with lower incident pain. This, combined with lower renal clearance of opioids,

Table 48-4

Principles of pharmacotherapy in palliative care

- Believe patient report of symptoms.
- Modify pathologic process when possible and appropriate.
- In terminally ill, avoid medications not directly linked to symptom control.
- Use a multidisciplinary approach.
- Consider nonpharmacologic approaches whenever possible.
- Engage participation of clinical pharmacist in treatment plan.
- Select drugs that can multitask (i.e., use haloperidol for agitated delirium and nausea).
- For pain, use adjuvant medications when possible (see Table 48-7).
- When using opioids, spare when possible (adjuvant medication, local or regional anesthetics, surgical interventions, etc.).
- Avoid fixed combination drugs.
- Avoid excessive cost.
- Select agents with minimum side effects.
- Anticipate and prophylax against side effects.
- For the elderly, the hypoproteinemic, theazotemic: “Start low and go slow.”
- Oral route whenever possible and practical.
- No IM injections.
- Scheduled dosing, not prn, for persistent symptoms.
- Stepwise approach. (See the World Health Organization Analgesic Ladder for pain. See Table 48-5.)
- Reassess continuously and titrate to effect.
- Use equianalgesic doses when changing opioids (see Table 48-5).
- Assess patient/family’s comprehension of management plan.

may result in greater potency of the prescribed agents. Severe pain crises are fortunately rare, but when they are inadequately addressed, can cause great and lasting distress (complicated grief) for loved ones who witness the final hours or days of agony. Such situations may require continuous administration of parenteral opioids. As death approaches and patients become less verbal, it is important to assess pain frequently, including the use of close observation for nonverbal signs of distress (e.g., grimacing, increased respiratory rate). Adequate dosing of opioid analgesics may require alternate route(s) of administration as patients become more somnolent or develop swallowing

Table 48-5

The World Health Organization three-step ladder for control of cancer pain³⁰

- Step 1: mild pain (visual analogue scale, 1–3)
Nonopioid ± adjuvant medication
- Step 2: moderate pain (visual analogue scale, 4–6)
Opioid for mild to moderate pain and nonopioid ± an adjuvant
- Step 3: severe pain (visual analogue scale, 7–10)
Opioid for moderate to severe pain ± nonopioid ± an adjuvant

difficulties. Opioids should not be stopped abruptly, even if the patient becomes nonresponsive because sudden withdrawal can cause severe distress.^{46,47}

Cognitive failure at the end of life is manifested in most patients by increasing somnolence and delirium. Gradually increasing somnolence can be accompanied by periods of disorientation and mild confusion, and it may respond to the reassuring presence of loved ones and caregivers with minimal need for medications. A more distressing form of delirium also can develop, manifested by increasing agitation that may require the use of neuroleptic medications. Increasing amounts of opioids and/or benzodiazepines may exacerbate the delirium (especially in the elderly).

Pronouncing Death⁴⁸

If the body is hypothermic or has been hypothermic, such as a drowning victim pulled from the water in the winter, the physician should not declare death until warming attempts have been made. In the hospital, hospice, or home setting, the declaration of death becomes part of the medical or legal record of the event. There are a number of physical signs of death a physician should look for in confirming the patient’s demise: complete lack of responsiveness to verbal or tactile stimuli, absence of heart beat and respirations, fixed pupils, skin color change to a waxy hue as blood settles, gradual poikilothermia, and sphincter relaxation with loss of urine and feces. For deaths in the home with patients who have been enrolled in hospice, the hospice nurse on call should be contacted immediately. In some states, deaths at home may require a brief police investigation and report. For deaths in the hospital, the family must be notified (in person, if possible). A coroner or medical examiner may need to be contacted under specific circumstances (e.g., deaths in the operating room), but most deaths do not require their services. However, the pronouncing physician will need to complete a death certificate according to local regulations. Survivors may also be approached, if appropriate, regarding potential autopsy and organ donation. Finally, it is important to accommodate religious rituals that may be important to the dying patient or the family. *Bereavement* is the experience of loss by death of a person to whom one is attached. *Mourning* is the process of adapting to such a loss in the thoughts, feelings, and behaviors that one experiences after the loss.⁴⁹ Although grief and mourning are accentuated in the immediate period around death, it is important to note that patients and families may begin the process of bereavement well before the time of death as patients and families grieve incremental losses of independence, vitality, and control. In addition to the surviving loved ones, it is important to acknowledge that caregivers also experience grief for the loss of their patients.^{50,51}

PROFESSIONAL ETHICS: CONFLICT OF INTEREST, RESEARCH, AND CLINICAL ETHICS**Conflict of Interest**

Conflicts of interest for surgeons can arise in many situations in which the potential benefits or gains to be realized by the surgeon are, or are perceived to be, in conflict with the responsibility to put the patient’s interests before the surgeon’s own. Conflicts of interest for the surgeon can involve actual or perceived situations in which the individual stands to gain monetarily by his or her role as a physician or investigator. In the academic community, monetary gain may not be the primary factor. Instead,

Table 48-6

Analgesics for persistent pain

DRUG	INITIAL DOSING (ADULT, >60 kg)	COMMENTS
Mild persistent pain, visual analogue scale (VAS) 1–3 Acetaminophen (Tylenol)	325–650 mg PO qid Maximum = 3200 mg/24 h	Use <2400 mg if other potentially hepatotoxic drugs taken. Acetaminophen contained in concurrent nonprescription medications can easily exceed maximum daily allowable dose.
Aspirin	600–1500 mg PO qid	Gastric bleeding, platelet dysfunction
Choline magnesium trisalicylate (Trilisate)	750–1500 mg PO bid	Useful for avoiding platelet dysfunction
Ibuprofen (Advil, Motrin)	200–400 mg PO qid Maximum = 3200 mg/24 h	Gastropathy, nephropathy, decreased platelet aggregation
Naproxen (Naprosyn)	250 mg PO bid Maximum = 1300 mg/24 h	Available as a transcutaneous gel
Moderate persistent pain, VAS 4–6 Hydrocodone (Vicodin, Lortab)	5–7.5 mg PO q4h	Most prescribed drug in the United States Acetaminophen in compounded drug limits use to moderate pain.
Oxycodone	5 mg PO q4h	Sold as single agent or compounded with aspirin or acetaminophen. Slow release form available (Oxycontin)
Severe persistent pain, VAS 7–10 Morphine	10 mg PO q2–4h 2–4 mg IV, SC q1–2h	Standard drug for comparison to alternative opioids. Avoid or caution when giving to the elderly, patients with diminished glomerular filtration rate, or liver disease. Slow release PO form available (MS Contin).
Hydromorphone	1–3 mg PO, PR q4h 1 mg IV, SC q1–2h	Suppository form available Oral dose forms limited to 4 mg maximum
Fentanyl, transdermal	12 µg/h patch q72h	Not for acute pain management. Do not use on opioid-naïve patients. Absorption unpredictable in cachectic patients.
Methadone	Consultation with pain management, clinical pharmacists, or palliative care/hospice services skilled in methadone use is recommended for those inexperienced in prescribing methadone.	Not a first-line agent, although very effective, especially for pain with a neuropathic component Very inexpensive Can be given PO, IV, SC, PR, sublingually, and vaginally Its long half-life makes dosing more difficult than alternative opioids and close monitoring is required when initiating Numerous medications, alcohol, and cigarette smoking can alter its serum levels Physicians who write methadone prescriptions for pain should specify this indication. Methadone use for drug withdrawal treatment requires special licensure.

Risk factors for NSAID-induced nephropathy include: advanced age, decreased glomerular filtration rate, congestive heart failure, hypovolemia, pressors, hepatic dysfunction, concomitant nephrotoxic agents. Dose reduction and hydration reduce risk.

Opioids compounded with aspirin or acetaminophen are limited to treatment of moderate persistent pain because of dose-limiting toxicities of acetaminophen and aspirin.

Slow-release preparations of morphine and oxycodone may be given rectally.

Timed-release tablets or patches should never be crushed or cut.

Opioid analgesics are the agents of choice for severe cancer-related pain. Sedation is a common side effect when initiating opioid therapy. Tolerance to this usually develops within a few days. If sedation persists beyond a few days, a stimulant (methylphenidate 2.5–5 mg PO bid) can be given.

Initiate bowel stimulant prophylaxis for constipation when prescribing opioids unless contraindicated.

Adjuvant or coanalgesic agents are drugs that enhance analgesic efficacy of opioids, treat concurrent symptoms that exacerbate pain, or provide independent analgesia for specific types of pain (e.g., a tricyclic antidepressant for treatment of neuropathic pain). Coanalgesics can be initiated for persistent pain at any visual analogue scale level. Gabapentin is commonly used as an initial agent for neuropathic pain.

No place for meperidine (Demerol), propoxyphene (Darvon, Darvocet, or mixed agonist-antagonist agents [Stadol, Talwin]) in management of persistent pain. Always consider alternative approaches (axial analgesia, operative approaches, etc.) when managing severe persistent pain.

Note: These are not recommendations for specific patients. The inter- and intraindividual variability to opioids requires individualizing dosing and titration to effect.

Source: Adapted with permission from Dunn GP: Surgical palliative care, in Cameron JL (ed): *Current Surgical Therapy*, 9th ed. Philadelphia: Elsevier, 2008. Copyright Elsevier.

Table 48-7

Examples of adjuvant medications for treatment of neuropathic, visceral, and bone pain^a

DRUG CLASS	INITIAL DOSING (ADULT, >60 kg)	COMMENTS
Tricyclic antidepressants Best for continuous burning or tingling pain and allodynia Efficacy for pain not due to antidepressant effect Dose generally less than that required for antidepressant effect Dose titrated up every few days until effect. Pain may respond to alternative antidepressants if no response to initial agent.	Amitriptyline 10–25 mg PO qhs Nortriptyline 10–25 mg PO qd Doxepin 10–25 mg PO qhs Imipramine 10–25 mg PO qd	Sedating properties may be useful for relief of other concurrent symptoms. Side effects may precede benefit. Avoid in the elderly due to anticholinergic side effects. Less anticholinergic effect
Anticonvulsants For shooting, stabbing pain	Gabapentin 100–300 mg PO qd. Titrate up rapidly as needed. Max: 1800 mg qd Carbamazepine 200 mg PO q12h Valproic acid 250 mg PO tid	Commonly used first-line agent. Generally well tolerated. Does not require blood level monitoring. Effective. Well studied. Requires blood monitoring.
Local anesthetics Systemic use requires monitoring. Nebulized local anesthetics (lidocaine, bupivacaine) can be used for severe, refractory cough.	Lidocaine transdermal patch 5%. Apply to painful areas. Max: 3 simultaneous patches over 12 h (each patch contains 700 mg lidocaine). Lidocaine/prilocaine topical. Apply to painful areas.	Systemic toxicity can result from applying more than recommended number per unit time and in patients with liver failure. Effective for postherpetic neuralgia.
Miscellaneous	Bisphosphonates (pamidronate, zoledronic acid) Calcitonin nasal spray Dexamethasone Radionuclides (Sr-89) Octreotide	For bone pain and reduced incidence of skeletal complications secondary to malignancy—best results in myeloma and breast cancer. Contraindicated in renal failure. Refractory bone pain For bone pain, acute nerve compression, visceral pain secondary to tumor infiltration or luminal obstruction by reducing inflammatory component of tumor For malignant bone pain secondary to osteoclastic activity. 4–6 wk delay in benefit. Requires adequate bone marrow reserve. For prognosis of more than 3 mo. Reduces GI secretions that contribute to visceral pain

^aRecommendations are based on experience of practitioners of hospice and palliative medicine and in some instances do not reflect current clinical trials. Source: Adapted, with permission from Dunn GP: Surgical palliative care, in Cameron JL (ed): *Current Surgical Therapy*, 9th ed. Philadelphia: Elsevier, 2008. Copyright Elsevier.

motivators such as power, tenure, or authorship on a publication may serve as potential sources of conflict of interest. For example, the accrual of subjects in research studies or patients in surgical series may ensure surgeons better authorship or more financial gains. The dual-role of the surgeon-scientist therefore needs to be considered because the duty as surgeon can conflict with the role of scientist or clinical researcher.

Research Ethics

Over the last three decades in the United States, the ethical requirements for the conduct of human subject research have been formalized and widely accepted. Although detailed informed consent is a necessary condition for the conduct of ethically good human subject research, other factors also determine whether research is designed and conducted ethically. Emanuel and colleagues⁵² described seven requirements for all clinical research studies to be ethically sound: (a) value—

7▶ enhancement(s) of health or knowledge must be derived from the research; (b) scientific validity—the research must be methodologically rigorous; (c) fair subject selection—scientific objectives, not vulnerability or privilege, and the potential for and distribution of risks and benefits, should determine communities selected as study sites and the inclusion criteria for individual subjects; (d) favorable risk-benefit ratio—within the context of standard clinical practice and the research protocol, risks must be minimized, potential benefits enhanced, and the potential benefits to individuals and knowledge gained for society must outweigh the risks; (e) independent review—unaffiliated individuals must review the research and approve, amend, or terminate it; (f) informed consent—individuals should be informed about the research and provide their voluntary consent; and (g) respect for enrolled subjects—subjects should have their privacy protected, the opportunity to withdraw, and their well-being monitored.⁵²

Special Concerns in Surgical Research

A significant issue for clinical surgical research is that it is often analyzed in a retrospective manner and not commonly undertaken in a prospective double-blind, randomized fashion. For a randomized trial to be undertaken, the researchers should be in a state of equipoise—that is, there must be a state of genuine uncertainty on the part of the clinical investigator or the expert medical community regarding the comparative therapeutic merits of each arm in a trial.⁵³ To randomize subjects to receive two different treatments, a researcher must believe that the existing data are not sufficient to conclude that one treatment strategy is better than another. In designing surgical trials, surgeons usually have biases that one treatment is better than another and often have difficulty maintaining the state of equipoise. As such, it is frequently difficult to demonstrate that a randomized trial is necessary or feasible, and treatment options that question the validity of clinical tenets are difficult to accept. Meakins has suggested that a slightly different hierarchy of evidence applies to evidence-based surgery.⁵⁴

A second major issue for surgical trials is whether it is ethically acceptable to have a placebo-controlled surgical trial. Some commentators have argued that sham surgery is always wrong because, unlike a placebo medication that is harmless, every surgical procedure carries some risk.⁵⁵ Others have argued that sham operations are essential to the design of a valid randomized clinical trial because, without a sham operation, it is

not possible to know if the surgical intervention is the cause of improvement in patient symptoms or whether the improvement is due to the effect of having surgery.^{56,57} Most surgeons readily agree that designing an appropriately low-risk sham surgical procedure would create problems for the surgeon-patient relationship in that the surgeon would need to keep the sham a secret.⁵⁸ In this sense, a sham surgical arm of a trial is very different from a placebo medication in that there cannot be blinding of the surgeon as to which procedure was undertaken. As a result, to have a sham surgery arm in a clinical trial, the interactions between the surgeon and the subject must be limited and the surgeon performing the procedure should not be the researcher who follows the subject during the trial. Despite difficulties with designing a surgical trial in which the surgeon could ethically perform a sham operation, there are specific circumstances that allow for placebo operations to be conducted, so long as certain criteria are met and are analyzed on a case by case basis.^{59,60}

Surgical Innovation and Surgical Research

An important issue is whether surgical innovation should be treated as research or as standard of care. Many of the advances in surgical technique and surgical technology have resulted from the innovations that individual surgeons have discovered or created during the course of challenging operations. As every patient is different and the surgeon is always trying to determine the best way to complete an operation, innovations have developed that have often moved the field of surgery forward.⁶¹ In the Korean and Vietnam wars, the military guidelines for the treatment of vascular injuries recommended ligation and amputation rather than interposition grafting of vascular injuries. Individual surgeons chose to ignore those guidelines and subsequently demonstrated the value of reconstructive techniques that ultimately became the standard of care. It is debated whether modifications in an accepted surgical technique based on the circumstances of an individual patient and the skill and judgment of an individual surgeon should require the same type of prior approval that enrollment in a clinical trial would warrant.⁶² However, if a surgeon decides to use a new technique on several occasions and to study the outcomes, Institutional Review Board approval and all other ethical requirements for research are necessary. These situations require strict oversight as well as explicit consent by the patient.⁶³ In particular, when developing new and innovative techniques, the surgeon should work in close consultation with his or her senior colleagues, including the chairperson of the department. Frequently, more senior individuals can provide sage ethical advice regarding what constitutes minor innovative changes in a technique vs. true novel research.

Compared to the formalized process for new drug approval by the Food and Drug Administration, the process for a surgeon developing an innovative operation is relatively unregulated and unsupervised.

Clinical Ethics: Disclosure of Errors

Disclosure of error—either in medical or research matters—is important, but often difficult (see Chap. 12). Errors of judgment, errors in technique, and system errors are responsible for most errors that result in complications and deaths. Hospitals are evaluated based on the number of complications and deaths that occur in surgical patients, and surgeons traditionally review their complications and deaths in a formal exercise known as

the *mortality and morbidity conference*, or *M&M*. The exercise places importance on the attending surgeon's responsibility for errors made, whether he or she made them themselves, and the value of the exercise is related to the effect of "peer pressure"—the entire department knows about the case—on reducing repeated occurrences of such an error. Although a time-honored ritual in surgery, the M&M conference is nonetheless a poor method for analyzing causes of error and for developing methods to prevent them. Moreover, the proceedings of the M&M conference are protected from disclosure by the privilege of "peer review," and the details are rarely shared with patients or those outside the department.

A report from the United States Institute of Medicine titled "To Err Is Human" highlighted the large number of medical errors that occur and encouraged efforts to prevent patient harm.⁶⁴ Medical errors are generally considered to be "preventable adverse medical events."⁶⁵ Given that medical errors clearly occur with some frequency, the question becomes what and how should patients be told of medical errors and what is the surgeon's ethical responsibility for this disclosure.⁶⁶

Disclosure of error is consistent with the ethical tenets of openness with patients and the involvement of patients in their care. In contrast, failing to disclose errors to patients undermines public trust in medicine and potentially compromises the treatment of the consequences of errors. In addition, failure to self-disclose medical errors can be construed as a breach of professional ethics, as it is a failure to act solely for the patient's best interests. Patients require information regarding medical errors so that additional harm can be avoided. In addition, information regarding a medical error may be needed so that patients can make independent and well-informed decisions about future aspects of their care. The principles of autonomy and justice dictate that surgeons need to respect individuals by being fair in providing accurate information about all aspects of their care—even the medical errors.

Disclosing one's own errors is therefore part of the ethical standard of honesty and putting the patient's interests above one's own. Disclosing the errors of others is more complicated and may require careful consideration and consultation. Surgeons sometimes discover that a prior operation has included an apparent error; an injured bile duct or a stenotic anastomosis may lead to the condition for which the surgeon is now treating the patient. Declaring a finding as an "error" may be inaccurate, however, and a non-judgmental assessment of the situation is usually advisable. When clear evidence of a mistake is at hand, the surgeon's responsibility is defined by his or her obligation to act as the patient's agent.

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49 chapter

Global Surgery

Raymond R. Price and Catherine R. deVries

Introduction	1955	Initiatives for Outreach and Engagement / 1963	Academic Partnerships / 1977
Defining Global Surgery	1956	International Organizations / 1963	Ethics / 1977
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Burden of Surgical Disease / 1957		Cancer Initiatives / 1970	The Future for Global Surgery 1978
Human Resources / 1960		Advanced Surgical Care for Resource-Poor Areas / 1976	
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INTRODUCTION

Modern surgery can save lives, help expand economies, and offer hope to individuals and communities. Prior to the acceptance and availability of aseptic technique to prevent or decrease infections, and improved anesthesia for controlling pain, surgery as a specialty was held in very low esteem. Over the last 100 years, surgery has developed into an elite discipline that not only provides opportunities for curing certain diseases, but fulfills a special role in preventing and mitigating disability.

Yet, surgery is currently unavailable to most people worldwide. The vast majority—90%—of the world's population receives only 10% of the surgical care delivered. Said another way, 90% of the world's surgical resources are consumed by the most privileged 10% of the world's population. More than 2 billion people lack access to even basic surgical care.¹ Very few surgical procedures occur in countries spending less than US \$100/ person on health care per year compared to countries spending greater than U.S. \$1000/ person (Fig. 49-1).²

Examples of disparities abound. In many countries, including the wealthiest, deep pockets of poverty coexist within cities replete with material resources. Tertiary level hospitals operate within eyesight of slums whose inhabitants have no access to even basic care. Most of the people without access—people in rural areas and in countries with poor infrastructure—are the very people most at risk for death or disability due to lack of surgical care. Often the poor accept and endure many painful and potentially correctable fatal conditions as a fact of life.³⁻⁶ Care for trauma and obstetrical emergencies are considered basic surgical needs but are absent in many rural regions. Other chronic conditions—often equally debilitating—progress to death or serious disability due to lack of available, safe surgery and anesthesia.

Many factors contribute to the disparity in access to surgical care. Poverty, a primary risk factor for all types of diseases, is a major obstacle hindering access to surgery. Healthcare professionals, including surgeons, migrate from areas of need due to a lack of infrastructure (hospitals, roadways, and stable electrical sources), limited supplies and equipment, lack of human

resources, few opportunities for professional development, and concerns for personal safety. Finally, the lack of information about the burden of surgical disease and surgery's impact on communities has led to misconceptions of policy makers that quality surgical care is cost prohibitive and too complex to be seriously considered a viable conduit for improving global health.^{7,8}

1► Disparities in care and outcomes are multidimensional, and no simple solution exists to improve access to appropriate and affordable surgical care. Yet, five major forces are reshaping priorities and strategies leading the charge for the globalization of surgical care:

1. *The epidemiologic transition of diseases* from primarily infectious to more chronic conditions;
2. *The mobile nature of the world's populations* allows more convenient travel opportunities for people to move freely between more isolated areas of the world leading to a more integrated global community;
3. *Ubiquitous information access* exponentially enabling universal participation in understanding and designing innovative opportunities for high-quality surgical care;
4. *A revolution for equity and human rights* where the world's poor are demanding benefits to surgical care similar to those found in developed countries;
5. *Recognition of the cost-effectiveness of surgical care*, and its potential to build economies, demonstrating the potential value of, including surgery in global health strategies.^{9,10}

The potential benefits of surgical care for economic productivity are astounding. Considering that the annual economic loss from road traffic injuries alone exceeds U.S. \$500 billion globally, a panel of expert economists at the Copenhagen Consensus of 2012, including four Nobel prize laureates, understandably prioritized strengthening surgical capacity as the eighth most cost-effective investment for addressing the world's current most pressing problems.^{8,11} Good health, which fosters productive economies and political stability, must include access to the full spectrum of health care, including surgical care to

Key Points

- 1▶ There are five major forces reshaping priorities and strategies for the globalization of surgical care:
 - a. The epidemiologic transition of diseases
 - b. The mobile nature of the world's populations
 - c. Ubiquitous information access
 - d. A revolution for equity and human rights
 - e. Recognition of the cost-effectiveness of surgical care
- 2▶ Understanding and addressing the necessary communication, energy and transportation technologies along with the underlying cultural context represent the foundation critical to implementing sustainable infrastructure necessary for appropriate surgical care.
- 3▶ The key components of the global surgery ecosystem include technology, education, community, healthcare, business, and multidisciplinary engagement between a variety of disciplines.
- 4▶ There has been a significant shift from communicable, maternal, neonatal, and nutritional causes to noncommunicable causes, many of which require surgical care.
- 5▶ Patients and their communities in low-middle income countries (LMICs) bear a much greater share of the burden of cancer than high-income countries.
- 6▶ Globally, trauma has become a leading cause of death and disability; 90% of trauma deaths occur in LMICs.
- 7▶ The burden of disease is greatest in areas where human resources—physicians, nurses, pharmacists, and other healthcare workers—are the least.
- 8▶ Surgery is gaining an increasingly recognized role for improving public health.
- 9▶ Surgery has a role in prevention as well as treatment.
- 10▶ The cost-effectiveness of various aspects of surgical care has allowed surgical initiatives to be included when prioritizing public health initiatives.
- 11▶ Developing advanced surgical capabilities in resource-poor countries has the potential to decrease overall cost and actually develop the infrastructure necessary to entice physicians and other healthcare workers to remain in their own countries.
- 12▶ Academic involvement in global surgery provides training for the next generation of surgical leaders.
- 13▶ Surgical innovations that consider cost as well as quality and design for challenging energy environments will foster equity in surgical care for LMICs.

“advance the quality of life for billions of citizens around the world.”⁸

This chapter examines the need for expanding surgical care globally, explores some of the seemingly insurmountable challenges, and presents potential guiding concepts along

with examples of successful strategies for sustainable surgical development.

DEFINING GLOBAL SURGERY

Global Surgery Ecosystem

To understand how surgery fits into healthcare systems and to understand its unique needs, it is helpful to consider global surgery as an ecosystem. The emerging field of global surgery considers surgical care to be a fundamental component of global health. As a system with both local and international scope, global surgery encompasses not just the medical and technical aspects of surgical care but also the societal and environmental context in which surgery is performed. Surgery as an ecosystem considers the diverse but interrelated systems that must be functional for quality surgical care to be delivered. Only part of these systems falls within the traditional training of surgeons. Yet, modern surgical care requires these systems to work in a coordinated fashion to support three priorities critical for expanding surgery globally—accessibility, affordability, and innovation (Fig. 49-2). Global surgery is a way to consider a “systems-based practice” beyond a single hospital or community for the benefit of people worldwide. Many of the interrelated components of this surgical ecosystem originate outside the hospital.

- 2▶ Disparities in surgical care have geographical, socioeconomic, and cultural components. Most people who live in major cities in northern and western hemisphere countries take for granted a functioning energy grid. The development of energy beyond major cities has enabled many wealthier communities to imagine, and indeed, to expect healthcare to be available at all times and to be affordable. Yet, a lack of reliable energy sources is a major limiting factor. Communication and transportation technologies, for example, the mobile phone and air and ground travel, have dramatically progressed

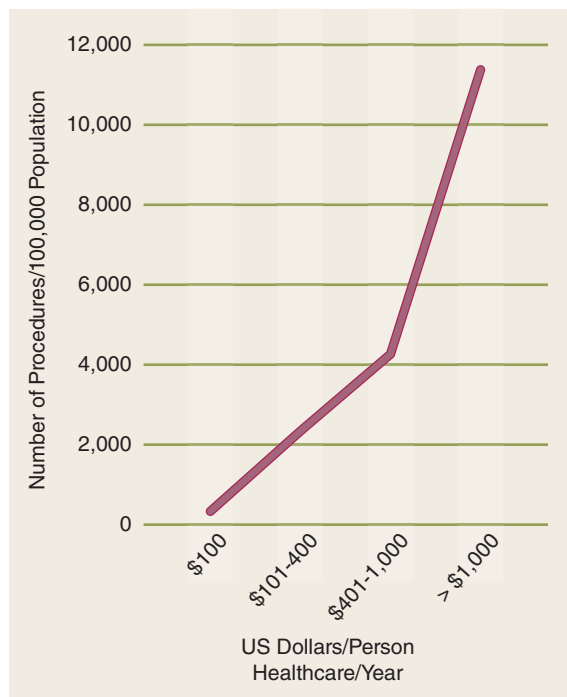


Figure 49-1. Worldwide distribution of surgical procedures. (Data from Weiser TG, Regenbogen SE, Thompson KD, et al. An estimation of the global volume of surgery: a modeling strategy based on available data. *Lancet*. 2008;372(9633):139-144. Illustration reproduced with permission from Intermountain Healthcare.)

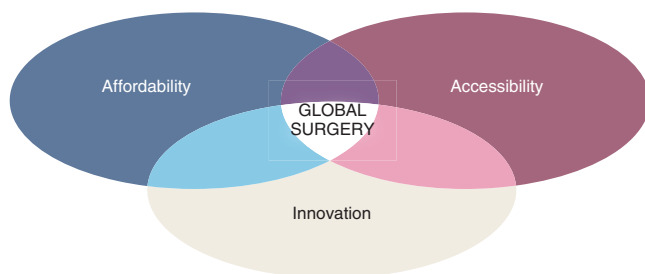


Figure 49-2. Global surgery priorities. (Reproduced with permission from University of Utah Center for Global Surgery and Intermountain Healthcare.)

in high- and middle-income countries but are still rudimentary in poor countries. Many of the current disparities in health care, particularly surgical care, are due to the lack of penetration of these technologies. Understanding and addressing the necessary communication, energy and transportation deficits as well as the underlying cultural nuances are necessary to support the sustainable development of surgical care (Fig. 49-3).

Electricity is necessary for all modern surgery. Anesthesia monitoring, OR lighting, cautery, suction, and patient warming devices all require sources of electricity that are stable, without huge electrical surges. Only in the last 50 years or so could stable electricity be expected in most wealthy cities. However, in rural areas of even wealthy countries, electricity remains unpredictable (Fig. 49-4).

In poorer countries, the cost and availability of electricity is frequently the limiting factor for more advanced diagnostic and therapeutic technology—from laboratories that require refrigeration to radiology in all of its various branches. Modern design for surgical devices has, for the most part, not taken into account the wide range of energy environments where surgery is practiced. Fragile instruments and monitors that cannot survive the rigors of the real working environment limit the types of surgery that can be provided.

Components of the Global Surgery Ecosystem. Improvements in energy, transportation, and communication are critical to support the growth of six key components of surgical care (Fig. 49-5).⁹ While building capacity within each component is important, it is the interaction between the components that creates a functioning, sustainable system.

When surgeons think of surgery, they usually think in terms of science and hands-on technical expertise. However, global

surgery requires a broader understanding of systems in other disciplines. Surgeons must work collaboratively with engineers and business leaders to develop technology that can function in lower resource environments. These innovations can provide a source of economic growth for the community, which in turn supports better health care.

No sustainable surgical system in the modern age can function without specialists in bioengineering, sterile process, supply chain, hospital safety and waste management. These often unappreciated colleagues make possible the daily practice of surgery. Similarly, specialists in anesthesia, nursing, and the diagnostic specialties of radiology, pathology, and laboratory services are fundamental to a fully functional surgical service.

Burden of Surgical Disease

Epidemiologic Transition of Disease. The population on Earth currently stands at more than 7 billion. While the rate of growth has slowed in recent years, projections estimate that the population will continue to grow to 9 billion by 2050.¹² When thinking about global surgery, it is helpful to step back from the individual and consider families, communities, and nations. Each entity has its unique cultural and economic history and geographic advantages or disadvantages. Each has its own system for addressing surgical care but operates within a larger ecosystem, including energy availability, telecommunications and social networks, an interdependent global economy, and local material resources.

Population characteristics are changing rapidly. According to United Nations estimates, the human population of the entire world is aging, even in low-income countries, and by 2050, 2 billion people will be over the age of 60. Currently, Asia is home to 55% of the world's population over the age of 60.¹³ Until recently, infectious diseases dominated public health strategy. Now with major scourges like polio isolated to relatively small regions of the world and HIV and malaria decreasing in their relative impact worldwide, chronic diseases and their complications, as well as the effects of aging, are gaining dominance in health care needs. Many of these chronic diseases are best approached by surgery.

The lack of metrics and paucity of data identifying the unmet burden of surgical need in many countries have been obstacles facing global surgery initiatives. The 2010 Global Burden of Disease Study was the first worldwide comprehensive burden of disease evaluation since the initial 1990 epidemiologic study. Using the disability-adjusted life years (DALY), a metric initially proposed for the 1990 study that captures both premature mortality and the prevalence and severity of illnesses, disease burdens were calculated for 291 causes in 21 regions of the world (including 187 countries) for 1990, 2005, and 2010 to enable identification of significant trends over time.¹⁴ While the global DALYs remained stable from 1990 to 2010, the study identified a significant shift from communicable, maternal, neonatal, and nutritional causes to noncommunicable causes (Fig. 49-6).¹⁵

In the 2006 *Disease Control Priorities 2nd edition*, the global burden of premature death and disability from surgically treatable conditions was estimated at 11% of the total global burden of disease.¹⁰ Recently, country-wide population surveys using the Surgeons OverSeas Assessment of Surgical Need (SOSAS) methodology identified a large unmet burden of surgical disease. In Sierra Leone, 25% of deaths of household members during the previous year might have been averted



Figure 49-3. Foundation for creating surgical infrastructure. (Reproduced with permission from Catherine R. deVries, M.D., University of Utah, and Intermountain Healthcare.)



Figure 49-4. Map of world electrification. (NASA, *Visible Earth*, <http://visibleearth.nasa.gov/view.php?id=79765>)

by timely surgical care; 25% of respondents also reported a current condition needing surgical attention.¹⁶ In Rwanda, in 2011, the SOSAS survey found 41.2% of the population had at least one operative condition during their life time; 6.4% of the population was found to have a current surgically treatable condition.¹⁷ Using the percentage of the population currently needing surgical care from Rwanda and Sierra Leone combined with the 2012 population in Sub-Saharan Africa of almost 900 million, there are between 56 million and 218 million people just in Sub-Saharan Africa needing surgical attention today! Untreated acute and chronic surgical conditions represent a significant unmet burden of disease that have major impact on the economies of these nations.¹⁸

Cancer. Patients and their communities in low- and middle-income countries (LMICs) bear a much greater share of the burden of cancer than high-income countries. The dramatic increase in the proportion of reported cancer cases in LMICs is a result of population growth, aging populations, and the decreased mortality from infectious diseases. In 1970, only 15% of newly reported cancer cases worldwide were from the developing world; by 2008, this proportion rose dramatically

to 58% and is expected to grow to 70% by 2030.¹⁹ Previously thought to be a disease almost exclusive to high-income countries, nearly two-thirds of the 7.6 million cancer deaths worldwide occur in LMICs. Mortality from cancer correlates inversely with a country's economy for certain treatable cancers, including breast, testicular, and cervical cancer—LMICs have higher case fatality rates than high-income countries (Fig. 49-7).^{19,20}

For example, breast cancer case fatality rates illustrate the great disparity in outcomes between regions. Case fatality rates in East Africa reach an unacceptable 59% compared to 19% in the United States.²⁰ In LMICs, patients have very limited access to screening. They present for care with much later stages of cancer. In Haiti, after the great earthquake, in 2010, and after the initial onslaught of orthopedic injuries, many aid organizations found themselves faced with the unmet underlying burden of disease, including late stage breast cancer and other tumors (Fig. 49-8).

Trauma. Trauma has become a leading cause of death and disability around the world; 90% of trauma deaths occur in LMICs.²¹ Approximately 32% more people die

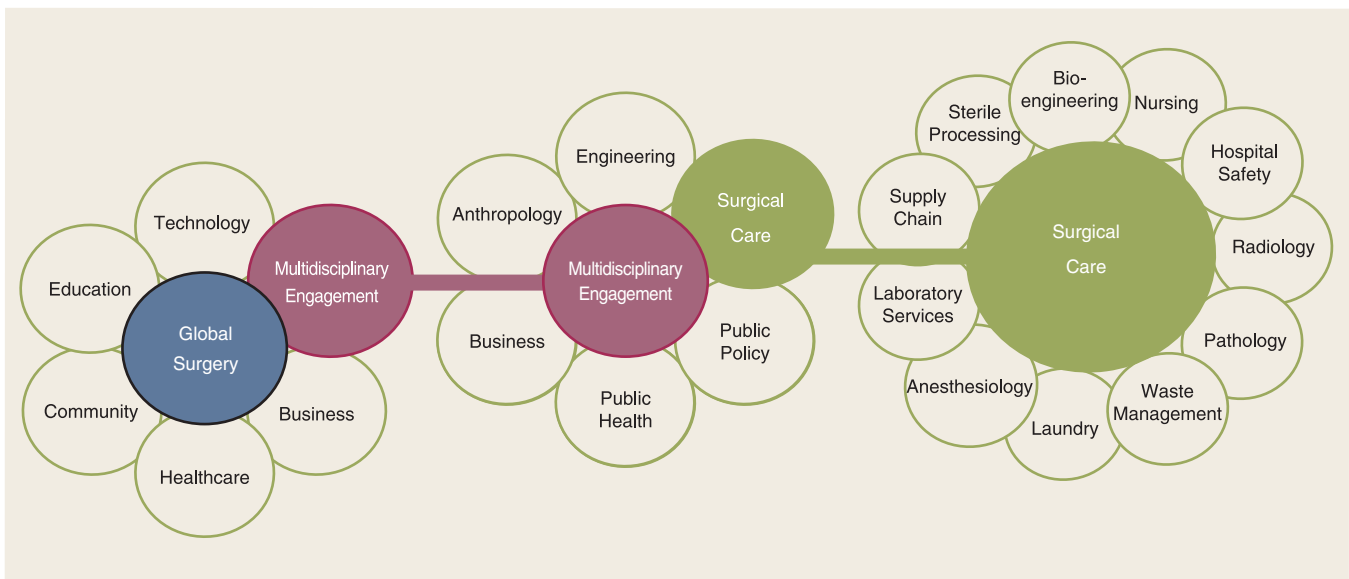


Figure 49-5. Key components of the global surgery ecosystem. (Reproduced with permission from Intermountain Healthcare.)

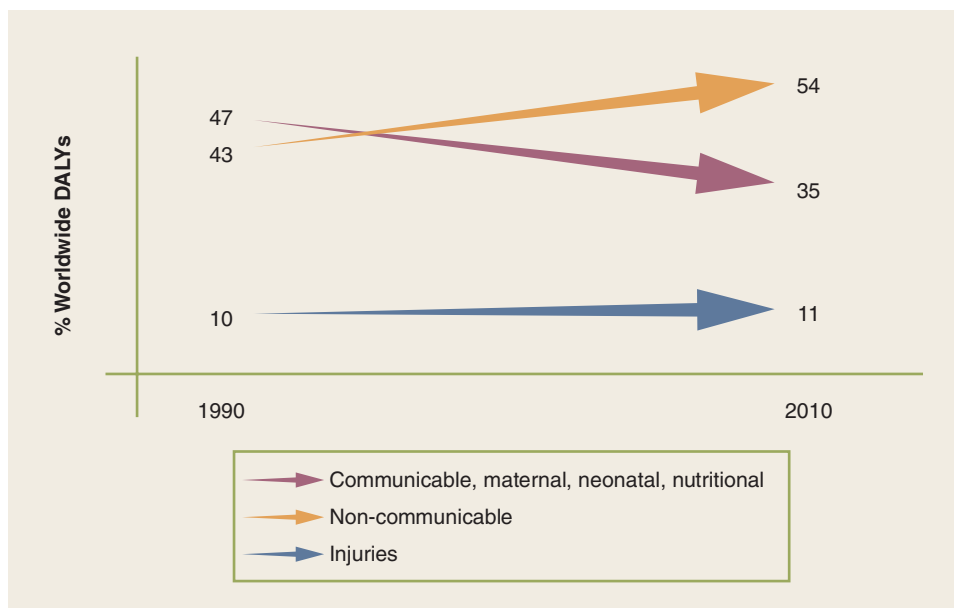


Figure 49-6. Shift in disease burden 1990–2010. (Data from Murray CJ, Vos T, Lozano R, et al. Disability-adjusted life years (DALYs) for 291 diseases and injuries in 21 regions, 1990–2010: a systematic analysis for the Global Burden of Disease Study 2010. *Lancet*. 2012;380(9859):2197–2223. Illustration reproduced with permission from Intermountain Healthcare.)

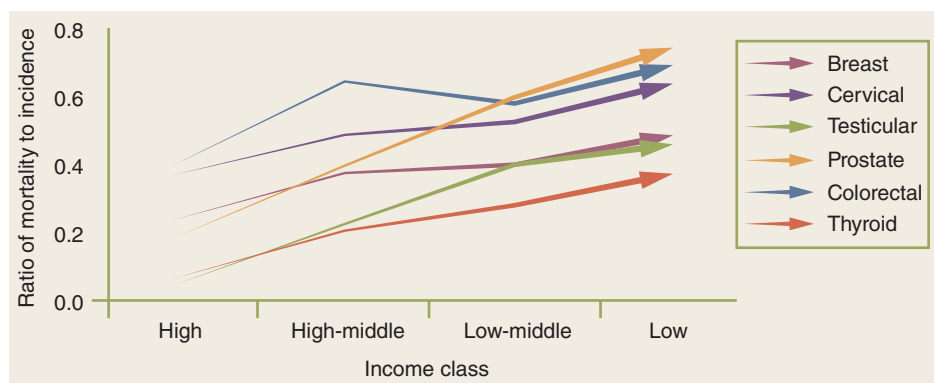


Figure 49-7. Ratio of mortality to incidence by solid tumor type and country income (2008). (Data from Farmer P, Frenk J, Knaul FM, et al. Expansion of cancer care and control in countries of low and middle income: a call to action. *Lancet*. 2010;376(9747):1186–1193. Illustration reproduced with permission from Intermountain Healthcare.)



Figure 49-8. Underlying unmet cancer burden in Haiti (2010). (Photos reproduced with permission from R. Dirk Noyes, MD; layout reproduced with permission from Intermountain Healthcare.)

Injuries and Violence: the Scale of the Problem

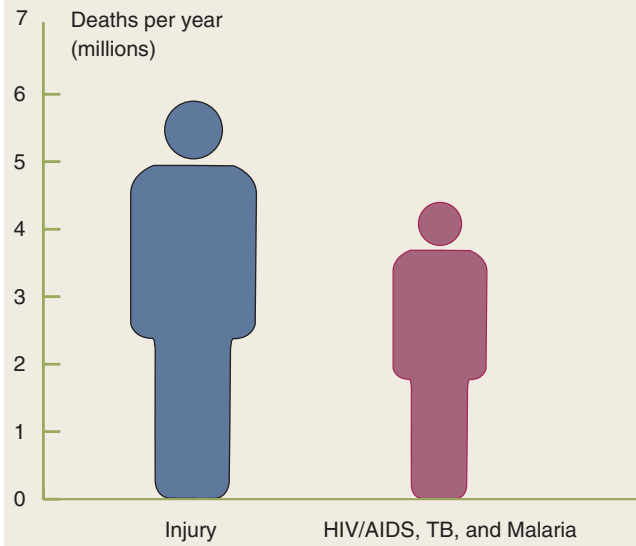


Figure 49-9. Injuries and violence: the scale of the problem. (*Injuries and violence: the facts*. Geneva, World Health Organization, 2010, http://www.who.int/violence_injury_prevention/key_facts/VIP_key_fact_1.pdf)

as a result from injuries than from malaria, tuberculosis, and HIV/AIDS combined representing 10% of the world's deaths (Fig. 49-9).^{22,23} In the United States, a patient presenting with an injury in a rural community has a higher mortality than those from an urban setting.²⁴ This disparity is much more pronounced in economically disadvantaged societies where seriously injured patients from road traffic accidents are twice as likely to die compared to similarly injured patients in a high-income setting (Fig. 49-10).^{22,25} Additionally, death is much more likely to occur in the pre-hospital settings for injured patients from low-income countries. The lack of integrated communication and

emergency transportation systems contribute to the pre-hospital risk, while the lack of infrastructure, supplies, and personnel contribute to in-hospital mortality.

Burns. Almost 11 million people worldwide sought medical or surgical care related to burns in 2004. However, the vast majority of burned people never present for medical care. Burns represent a significant cause of death as well as disability globally.²⁶ The vast majority of deaths from fires (95%) occur in LMICs. Burns result in nearly 200,000 deaths each year from fires while other forms of burns, including scalds and electrical burns, represent another significant source of death and disability. Women and children in LMICs are most likely to be burned in domestic kitchens; men are more likely to be burned in the workplace. The economic and social impact from long hospitalizations and from the resulting disfigurement provides a significant negative stigma causing ostracism and rejection.

Of all the forms of trauma worldwide, burns are the only type that predominantly afflicts women and children. Southeast Asia accounts for 27% of the burn-related deaths worldwide; 70% of people dying from burns in the region are women.²⁷ Cooking on wood, charcoal, or low kerosene stoves also puts children at risk, particularly from scalding (Fig. 49-11). Small children in the WHO African region have triple the number of burn deaths as children worldwide. Contrast this with the United States, where more burns and burn deaths affect men.

People living in rural areas suffer disproportionately because there are fewer facilities capable of managing the acute and chronic aspects of burn management and because the population is generally poorer. Surgical grafting and management of contractures is often best done in specialized burn centers, but these are rare in LMICs. Telemedicine has been shown to be effective in managing burns and preventing complications.²⁸

Human Resources

7▶ The greatest burden of disease occurs in areas where human resources—physicians, nurses, pharmacists, and other healthcare workers—are scarce (Fig. 49-12).²⁹ The proportion of physicians is low both in high population areas and in areas

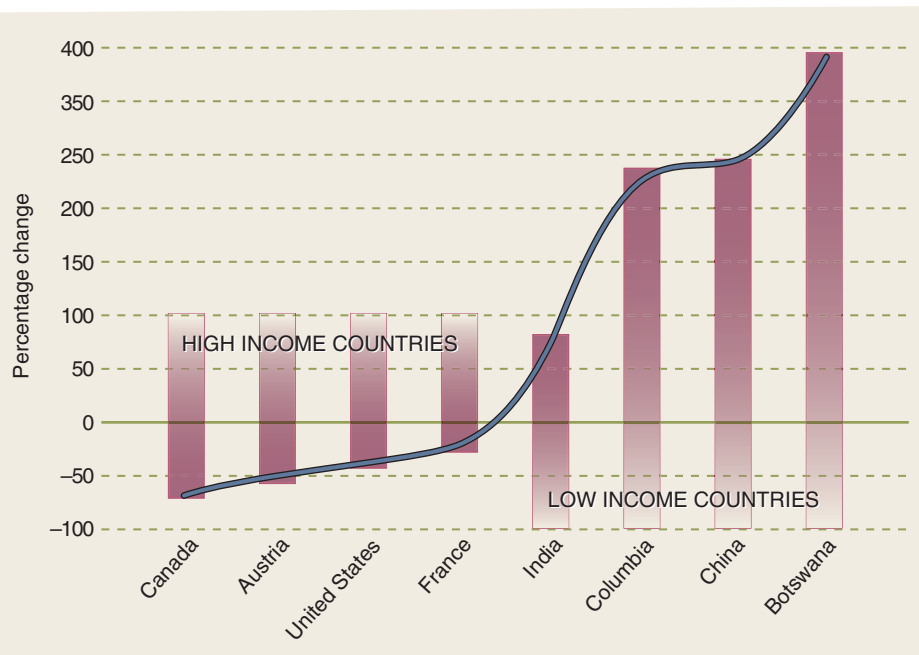


Figure 49-10. Change in traffic fatality risk (deaths/10,000 persons), 1975-1998). (Data from Kopits E, Cropper M. *Traffic fatalities and economic growth*. *Accid Anal Prev*. 2005;37(1):169-178. Illustration reproduced with permission from Intermountain Healthcare.)



Figure 49-11. Domestic kitchen: risk factor for burns in women and children in LMICs. (Reproduced with permission from James H. Kenney, Jr.)

where the population is growing most rapidly (Fig. 49-13).^{30,31} Fully trained surgeons and anesthesiologists comprise only a small proportion of the total number of the Human Resources in Health (HRH). In the Eastern Mediterranean, Southeast Asia, and Africa, HRH per 1000 people falls below the WHO minimum threshold (Fig. 49-14).²⁹ Many countries in Africa—for example Tanzania and Ethiopia—have only 0.6 surgeons per 100,000 population while the United States and Canada have 51 and 26 surgeons per 100,000 population, respectively.³² To provide the same concentration of surgeons in East Africa that currently exists in Canada would require training an estimated additional 42,000 surgeons.³³

Primary care physicians, nurses, midwives, or advanced care practitioners (ACPs) provide much of the basic surgical and anesthetic care in LMICs. Where regulations allow, “task shifting,” or training ACPs to deliver surgery and anesthesia services previously allowed only under the purview of fully trained specialists, can provide expanded access to care.³⁴⁻³⁶ Non-M.D. practitioners, variously known as *assistant medical officers* (AMOs) or “*tecnicos de cirurgia*” in Mozambique, often have extensive operative experience, including obstetrical care and are the primary providers of surgical care in a region.³⁷⁻³⁸ Task shifting to ACPs also occurs in the United States and other countries where they fill a need otherwise unmet by specialists

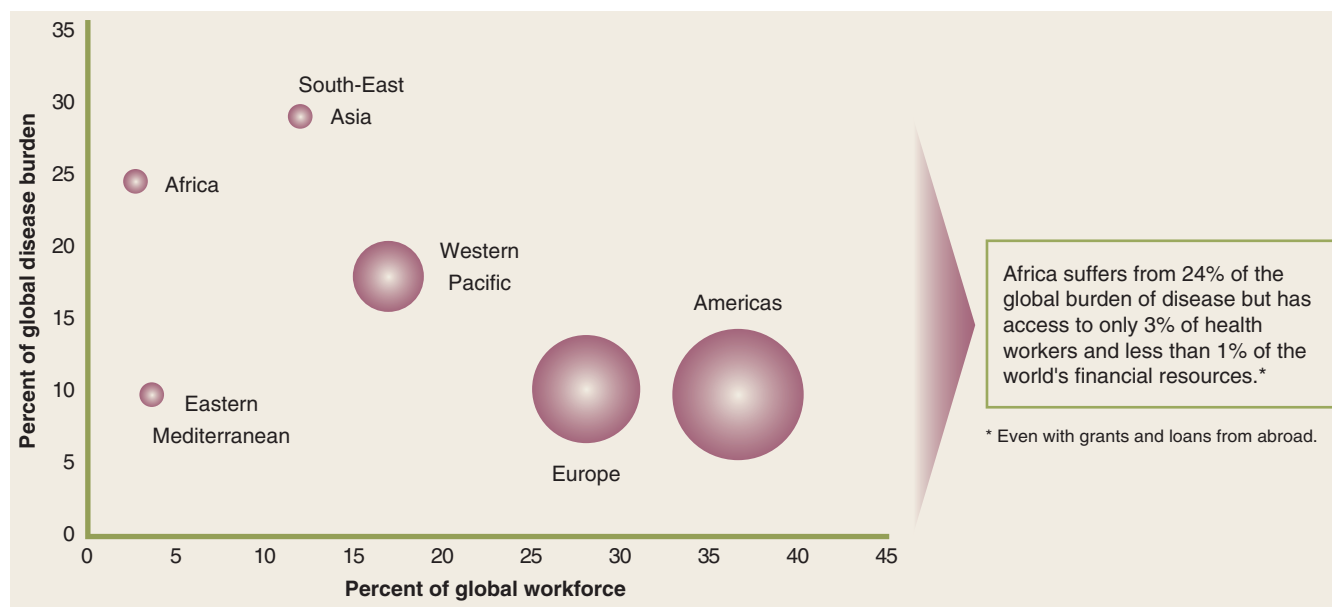


Figure 49-12. Distribution of healthcare workers by burden of disease in WHO regions. (Redrawn from Fig 5.1, *The Business of Health in Africa* (29) by permission. Reproduced with permission from Intermountain Healthcare.)

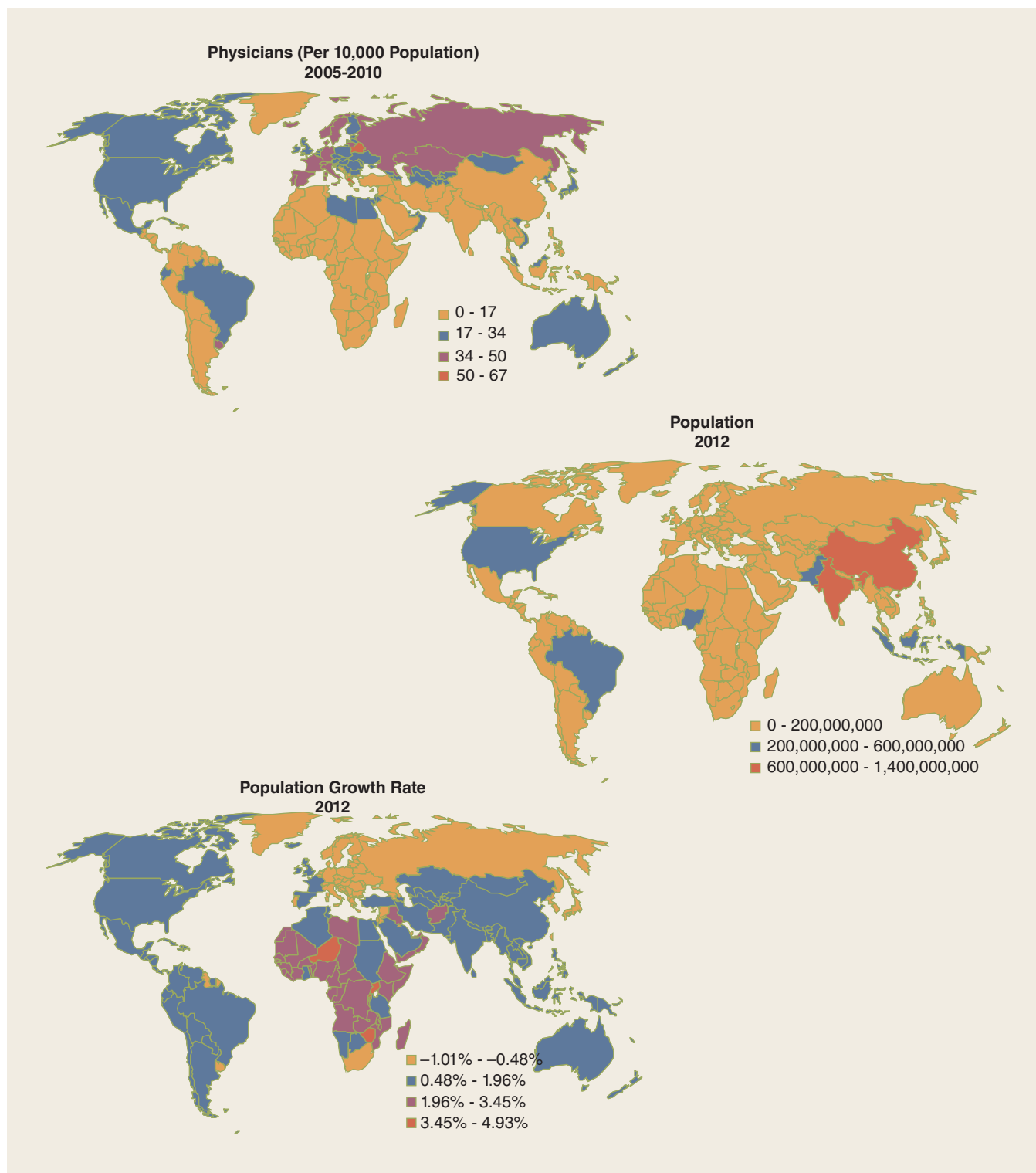


Figure 49-13. Number of physicians, world populations, and world population growth rates. (Figure Created from Data: Number of physicians per 10,000 population, 2005-2010, WHO, World Health Statistics 2012, available at: http://www.who.int/gho/publications/world_health_statistics/2012/en/index.html. See also, WHO, Global Health Observatory, available at: <http://www.who.int/gho/database/en/>; Population 2012, Sources: CIA, The World Factbook, available at: <https://www.cia.gov/library/publications/the-world-factbook/>.)

even in major tertiary care centers.³⁹ However, concerns about the quality of care, lack of adequate supervision, and the effect on prestige and professional development for specialists and ACPs, continue to be topics for debate.⁴⁰

Migration of practitioners to economically and culturally favorable locales is universal and not restricted to low-resource countries.⁴¹ However, the net impact on poor countries

is greater. In a 2004 study, more than 23% of U.S. physicians received their medical training from other countries; of these 64% were from low-income countries.⁴² Investments in training greater numbers of doctors in these countries, including surgical specialists, have been only partially successful in meeting the demand in poor countries. Until economic conditions improve or opportunities for professional development increase,

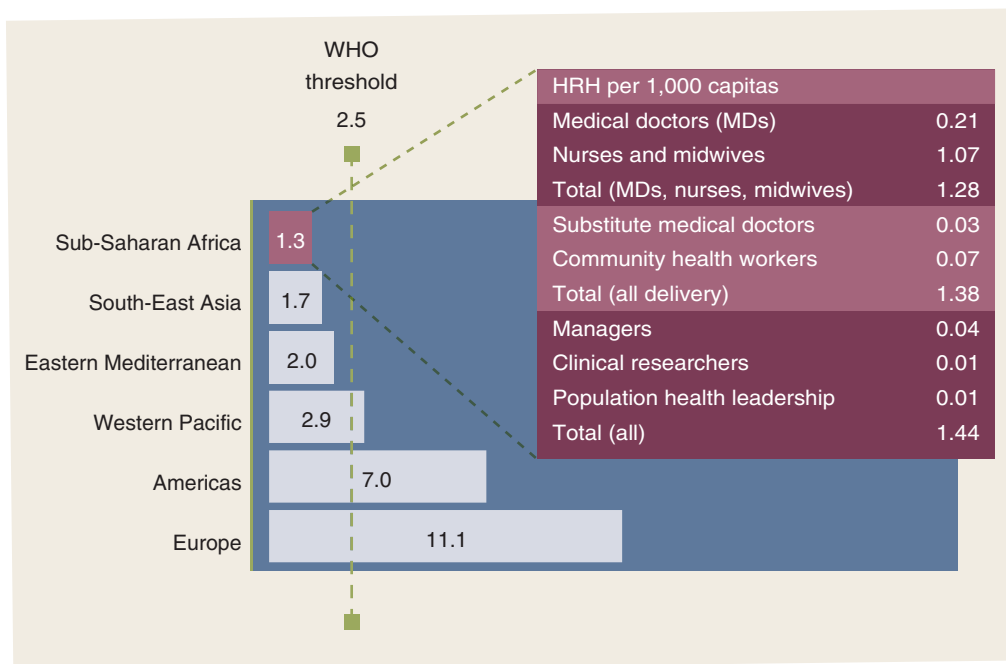


Figure 49-14. Human resources for health (HRH) by WHO region, 2006. (Redrawn from Fig 5.2, *The Business of Health in Africa* (29) by permission. Reproduced with permission from Intermountain Healthcare.)

and incentives enticing migration of health care workers to high-income countries abate, it is unlikely that the most skilled practitioners will remain in resource-poor areas beyond their immediate obligations.⁴³⁻⁴⁷

STRATEGIES FOR DEVELOPMENT

Initiatives for Outreach and Engagement

Many models for outreach and engagement have had a positive impact on the accessibility of surgery. Organizations participating in outreach are guided by a wide range of motivations and resources (Fig. 49-15). Some organizations are purely humanitarian and service oriented; others are primarily educational. Some even use the promise of healthcare to advance political, religious, or personal agendas.

Responding to the challenges of disparities, new generations of students, faculty, philanthropists, private industry leaders and policy makers have demonstrated a growing passion to address global surgery as part of global health. Prior to 1984 only 0.32% of physicians and 0.12% of nurses were involved in international health (either paid or volunteer).⁴⁸ Recently, interest in global health has exploded among medical students in the United States. A 2009 survey indicated that 25% of U.S. medical students have traveled to LMICs for clinical and research electives. At some medical schools the number has risen to over 50%.^{49,50} In 2004, 40% of medical students in the United Kingdom spent their 6 to 12 week elective rotation in developing countries.⁵¹ A structured questionnaire was administered anonymously to all American College of Surgeons resident members. Approximately 94% of the respondents were general surgery residents, and 92% were interested in an international elective with many planning to volunteer in the future.⁵²

Many patients have benefited from the multitude of service-oriented volunteer “missions” providing much needed surgical care that would otherwise have been unavailable. While

volunteerism and medical missions are laudable activities, they are not a sustainable solution to long-term manpower shortages for health.⁵³ Comprehensive initiatives are also necessary to engage local healthcare professionals and organizations, governments, and academic institutions to build capacity at home.⁵⁴

International Organizations

United Nations (UN). Committed to maintaining international peace, developing friendly relations between nations, and promoting better standards of living (conquering hunger, disease, and illiteracy) and human rights, representatives from 51 nations in 1945 signed the United Nations Charter at the United Nations Conference on International Organization held in San Francisco, California.⁵⁵ There are now 193 member states.⁵⁶ The UN promotes a social justice agenda advocating for worldwide health, engagement of philanthropies and civil society in global health initiatives, and supports the Millennium Development Goals (MDGs).

Millennium Development Goals (MDGs). Leaders from 189 countries gathered at the UN headquarters in September 2000 and agreed on eight specific “Millennium Development Goals” (Table 49-1).⁵⁷ Some have argued that strengthening basic surgical care at district level hospitals is critical to reaching MDGs 4, 5, and 6 (reducing child and maternal mortality and halting and reversing the spread of AIDS).^{6,58} In poor countries, the enormous shortfalls in infrastructure, and human and material resources severely limits the capabilities to provide access to life-saving and life-changing services such as timely Cesarean-section, control of peri-partum hemorrhage, appropriate care for pediatric trauma, and treatment for a multitude of congenital diseases.^{3,59-64} While the evolution of public policy has been slow to accept surgical care as integral to poverty reduction and public healthcare, surgeons are actively campaigning for and joining the process of negotiating for inclusion of surgical care development into the new post-2015 to 2030 MDGs.⁶⁵

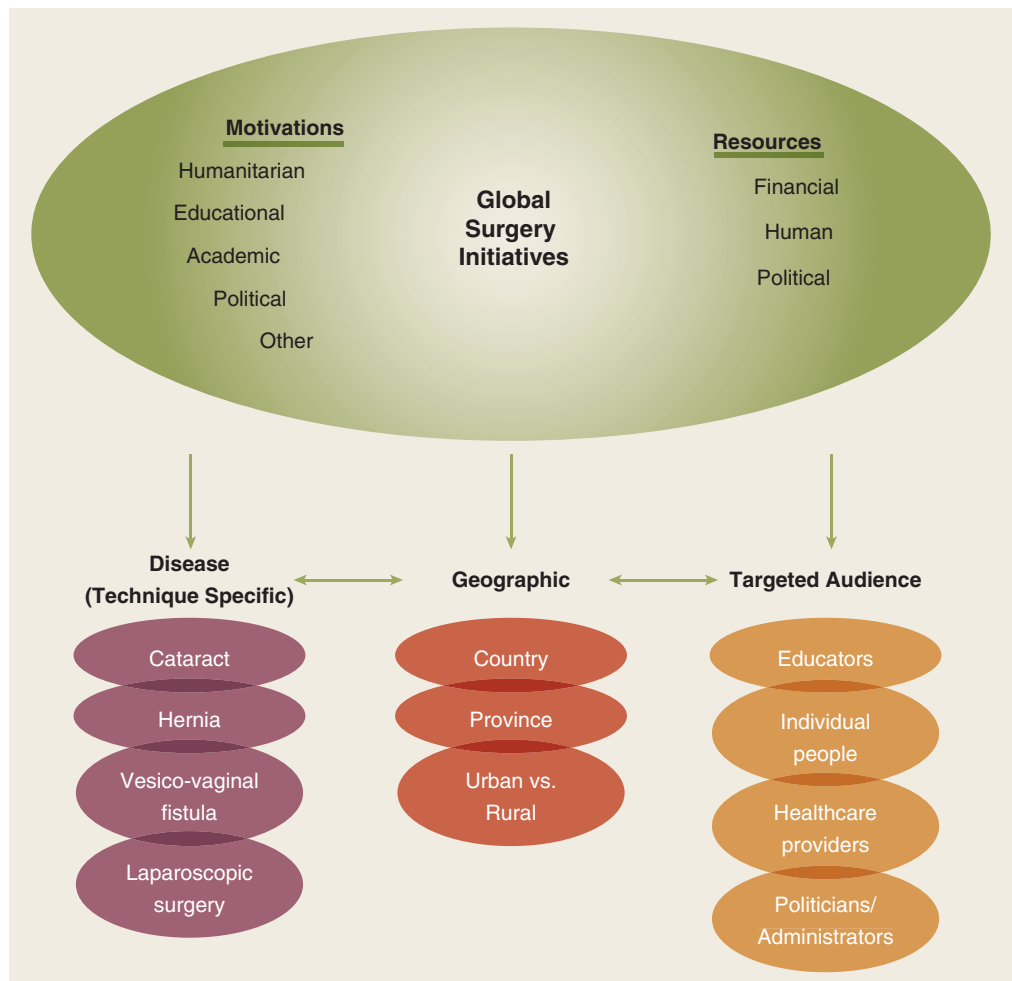


Figure 49-15. Global surgery initiatives. (Illustration reproduced with permission from Intermountain Healthcare.)

World Health Organization (WHO). The initial UN Conference in 1945 voted to establish a new international health organization. The Constitution of the World Health Organization (WHO) was approved and ratified in 1948.⁵⁵ The first World Assembly in 1948 established malaria, tuberculosis, venereal diseases, maternal and child health, sanitary engineering, and nutrition as WHO priorities. One of the WHO's greatest public health stories is the worldwide eradication of smallpox that began with the USSR proposal for the WHO-led program in 1958 culminating in the last identified case in Somalia in 1977.

Table 49-1

Millennium development goals 2000–2015

1. Reduce by half the number of people who suffer from hunger and whose income is < \$ 1/ day
2. Provide universal primary education
3. Promote gender equality
4. Reduce mortality rate for children < 5 years by two-thirds
5. Reduce maternal mortality rate by three quarters
6. Halt and reverse the spread of AIDS, malaria, tuberculosis, and other major diseases
7. Improve the environment
8. Strengthen the global partnership for development.

Data adapted from Millennium Development Goals. <http://www.undp.org/content/undp/en/home/mdgoverview/>

While the disease burden from communicable diseases has abated in large part from these successful international cooperative interventions, little has been done to address the growing global burden of surgical disease. Despite the laudable 1978 Declaration of Alma Alta that expressed the need for urgent action for the world community to protect and promote the health for all people, the declaration did so by crowning primary health care as the key to achieving the goal of health for all—which was then accepted by the member countries in the World Health Organization.⁶⁶ Although the Alma-Ata slogan “Health for all by 2000” did not materialize, it did galvanize efforts for global partnerships for healthcare improvements and poverty reduction.

The Violence and Injury Prevention Program (VIP) and the Global Initiative for Emergency and Essentials Surgical Care (GIEESC) are two programs related to surgery within the WHO that began before 2008. But, as a response to a growing recognition of the significant unmet surgical need, in 2008, the WHO for the first time included basic surgery as a component for community primary health care (Fig. 49-16).⁶⁷

The Global Initiative for Emergency and Essential Surgical Care (GIEESC). The Clinical Procedures (CPR) team in the WHO Department of Essential Health Technologies (EHT) convened a multidisciplinary group of experts from various surgical disciplines, professionals and civic leaders from national and international organizations, and representative from various WHO departments in December 2005 in Geneva, Switzerland, to formally organize the GIEESC.⁶⁸ GIEESC's main aim was

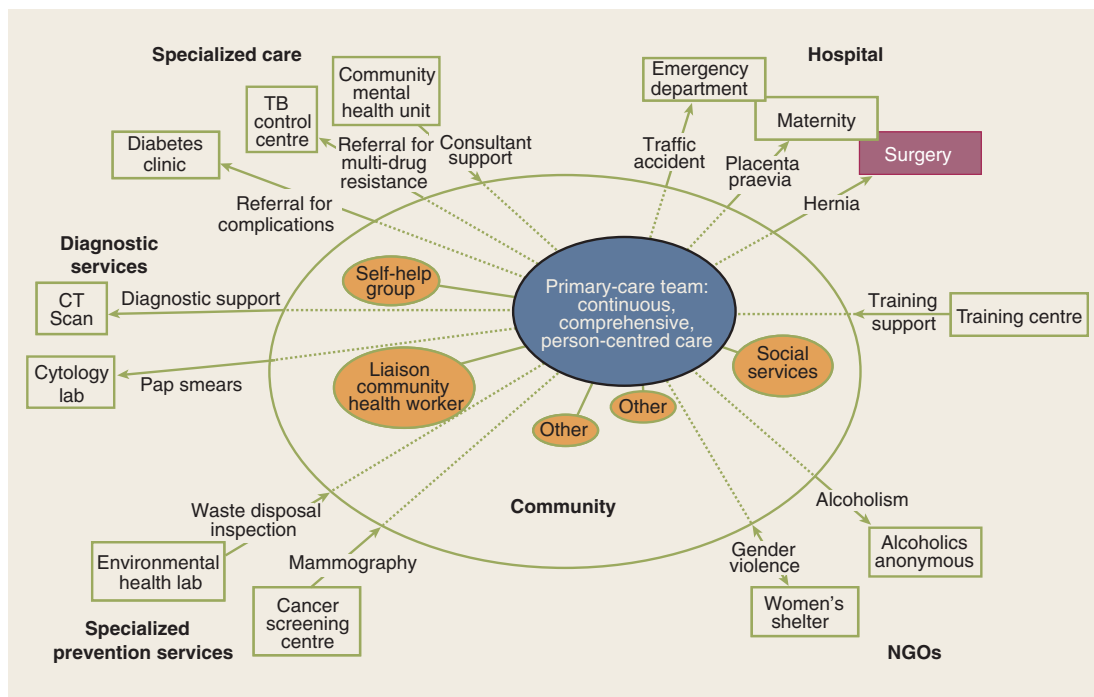


Figure 49-16. Emergency and essential surgery: an integral component of primary care. (*The World Health Report 2008, Primary Health Care Report, Now More Than Ever*, p. 55, Figure 3.5. <http://www.who.int/whr/2008/en/>)

to assist member states with capacity strengthening in the safe and appropriate use of emergency and essential surgical care (procedures, equipment) at resource-limited healthcare facilities through training and education programs. The training program was built around the WHO “Integrated Management of Emergency and Essential Surgical Care (IMEESC)” tool kit.⁶⁹ The tool kit included best practice protocols, guidelines on policies, training curriculum, emergency equipment, teaching slides, and

monitoring and evaluation instructions. Additionally, low-cost editions of the manual *Surgical Care at the District Hospital* have been made available in local languages. A Mongolian edition facilitated early expansion of GIEESC throughout the country. Mongolia has improved basic infrastructure, human resources and capabilities; and the use of the tool kit system has led to its incorporation into the countrywide healthcare plan.⁷⁰ (**Box:** Mongolia GIEESC)

Mongolia GIEESC

The WHO situational analysis tool developed in 2007 to assess the availability of emergency and essential surgical care (EESC) at individual health facilities has been utilized in 35 different countries documenting the limited infrastructure, human resources, procedures, equipment and supplies available for even basic EESC.⁶⁹ For example, there were no trained surgeons or anesthetists at 44 first referral hospitals in Mongolia.³ Only 66% of the facilities had electricity and 45% had running water (Fig. 49-17).

Most facilities lacked any policy for EESC, disaster preparedness, basic equipment to provide EESC, or any access to training for EESC. Adopting a health systems strengthening approach to rectify these glaring deficiencies, Mongolia implemented a nationwide EESC program involving 14 of the 21 provinces (Aimags) from 2004 to 2010 (Fig. 49-18).⁷⁰ In six years, dramatic improvements in short-term process measures were identified using the WHO Monitoring and Process form: 57.1% increase in availability of emergency rooms; 59.1% increase in the supply of emergency tool kits; and a 73.6% increase in the recording of emergency cases (Figs. 49-19 and 49-20).⁷⁰ More important, countrywide morbidity and mortality dropped significantly (Fig. 49-21).⁷¹



Figure 49-17. First Level (Soum) Hospital. (Photos reproduced with permission from Raymond R. Price MD. Layout reproduced with permission from Intermountain Healthcare.)

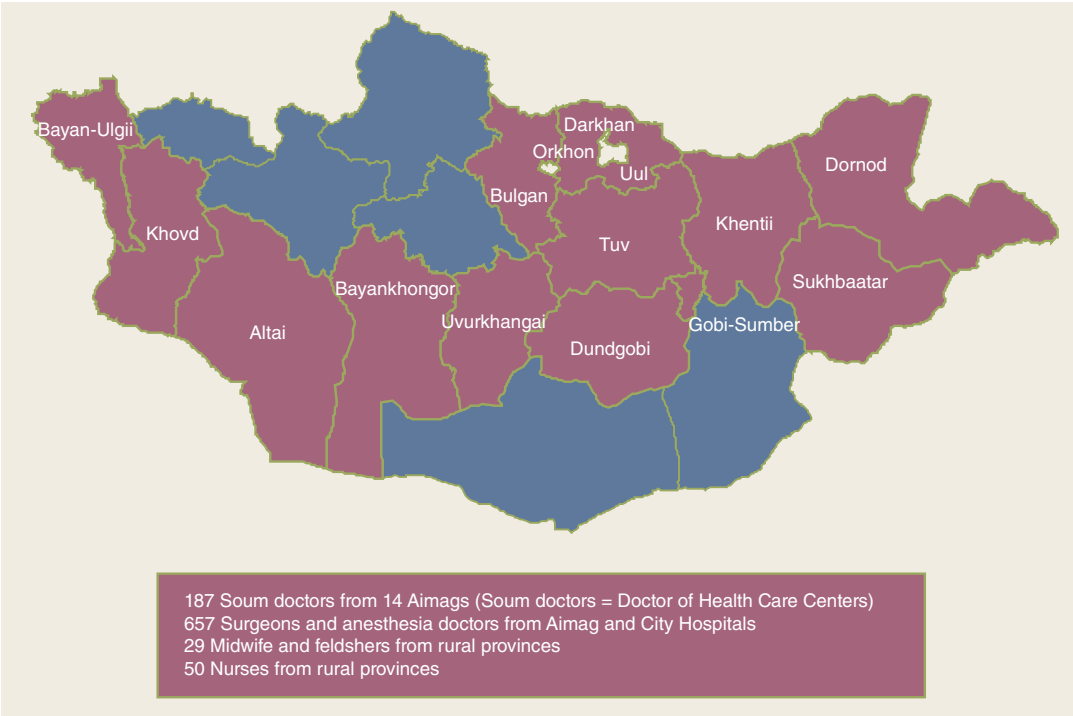


Figure 49-18. EESC Project: Mongolia 2004–2010. (Henry JA, Orgoi S, Govind S, Price RR, Lundeg G, Kehrer B. Strengthening Surgical Services at the Soum (First-referral) Hospital: The WHO Emergency and Essential Surgical Care (EESC) Program in Mongolia. *World J Surg.* 2012;36(10):2367, Fig. 2, With kind permission from Springer Science and Business Media.)

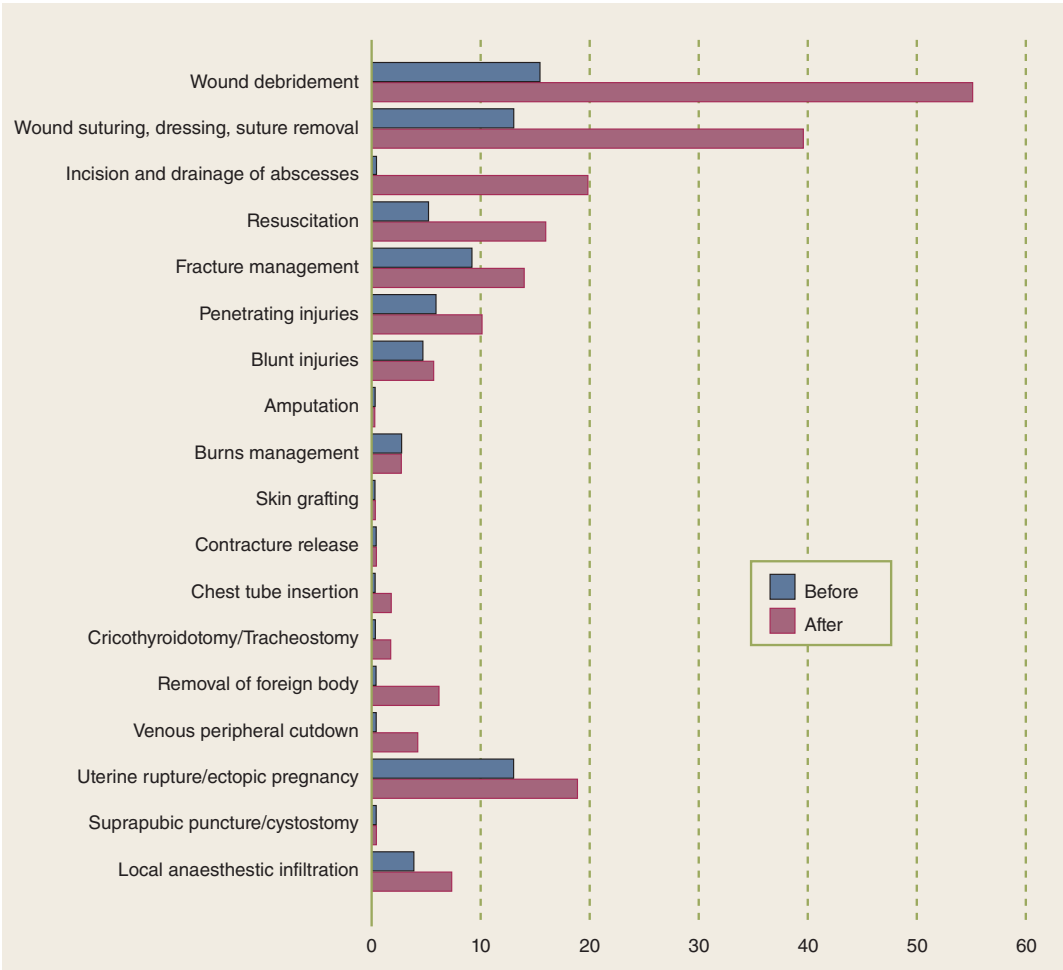


Figure 49-19. Surgical procedures performed 1-2 years Post-training (13 soum hospitals evaluated). (Henry JA, Orgoi S, Govind S, Price RR, Lundeg G, Kehrer B. Strengthening Surgical Services at the Soum (First-referral) Hospital: The WHO Emergency and Essential Surgical Care (EESC) Program in Mongolia. *World J Surg.* 2012;36(10):2367, Fig. 6, With kind permission from Springer Science and Business Media.)

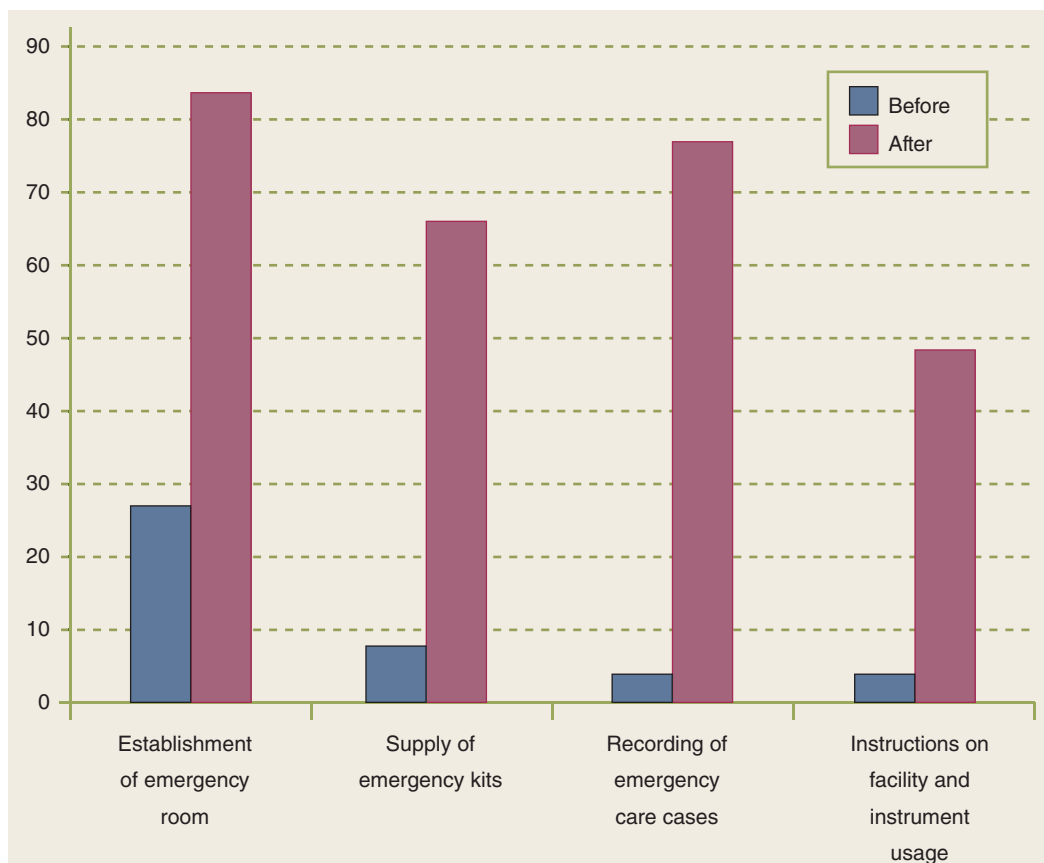


Figure 49-20. Pilot Soum hospitals' evaluation 2 years post-training. (Henry JA, Orgoi S, Govind S, Price RR, Lundeg G, Kehrer B. *Strengthening Surgical Services at the Soum (First-referral) Hospital: The WHO Emergency and Essential Surgical Care (EESC) Program in Mongolia*. World J Surg. 2012;36(10):2367, Fig. 5, With kind permission from Springer Science and Business Media.)

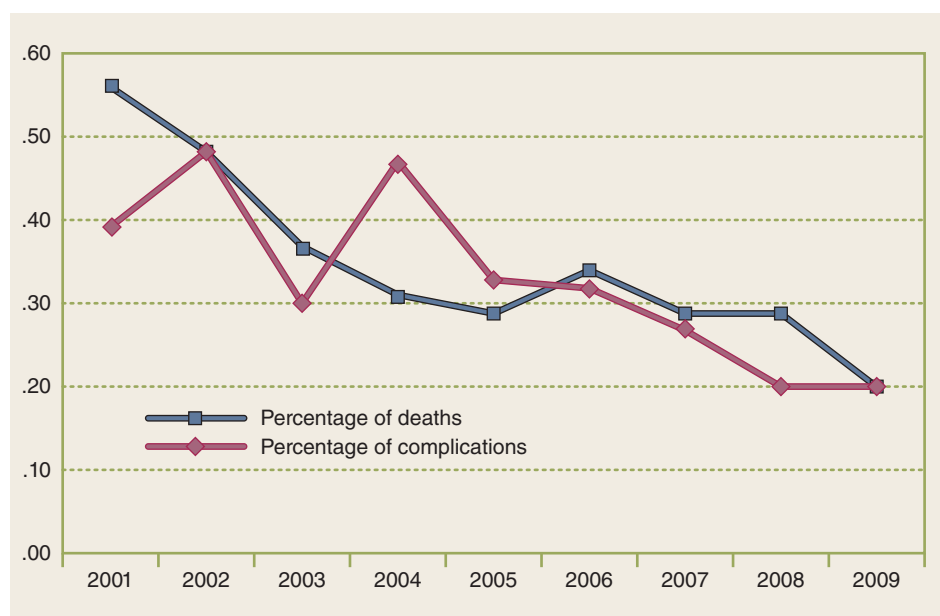


Figure 49-21. Surgical morbidity and mortality: Mongolia 2001–2009. (Adapted from *Indicators of Surgical Operation (Mongolia 2001–2009)*. 2010 [cited 2011 November 2]; Available from: www.doh.gov.mn. Illustration reproduced with permission from Intermountain Health-care.)

Violence and Injury Prevention (VIP). The Violence and Injury Prevention (VIP) program promotes numerous activities to assist countries to prevent and mitigate the consequences of violence and injury.⁷² While injury prevention is paramount, VIP provides guidance for strengthening trauma systems in countries of all economic levels to improve emergency care and rehabilitation. VIP also encourages development of systematic data collection and analysis to better guide appropriate interventions. Prevention programs include the WHO Helmet initiative while the Essential Trauma Care Project (ESTC) creates standards for the care of injured patients and promotes systematic capacity building.

WHO Safe Surgery Saves Lives Initiative. Surgeons have always sought ways to prevent peri-operative complications. Aseptic technique, one of the greatest forms of prevention in surgical care, requires vigilant reinforcement to prevent serious wound infections. In resource-limited areas inadequate pre-, intra-, and post-operative monitoring, lack of critical medications, and poor documentation can be severely lacking placing patients at increased risk for serious complications. The WHO Safe Surgery Saves Lives Initiative is a worldwide attempt to prevent peri-operative complications.⁷³

Deaths from surgery occur at 0.4% to 0.8% globally; however, they may exceed 5% to 10% in developing countries. There are about 1 million deaths and 7 million disabling complications related to surgery worldwide, 50% of which are estimated to be preventable. The WHO Safe Surgery Saves Lives initiative targets preventable surgical injuries.⁷³ The initiative identified 10 basic and essential objectives that can help prevent peri-operative injuries (Table 49-2).⁷⁴ A three-stage simple checklist (initiated as the patient entered the operating room, just before the procedure, and just prior to the patient leaving the room) implemented in 8 countries from high-, middle-, and

low-income countries found a 50% reduction in the failure to meet basic safety standards resulting in a 50 % decrease in mortality (Fig. 49-22).⁷⁵

Global Surgery and Public Health

8▶ Surgical care is increasingly recognized as an integral component of public health. Traditional public health teaching portrays surgery as the antithesis of public health: treating the individual instead of the community, reactionary instead of preventative, and too expensive especially for countries with developing economies. Yet in reality, surgery and public health priorities overlap in many areas (Fig. 49-23). For example, providing *access* to obstetrical care or birth attendants for every delivery could *prevent* the majority of vesico-vaginal fistulas and markedly decrease the most common cause of maternal death—hemorrhage—for entire communities.

Even after Learmonth presented his landmark lecture in 1949 “The Contributions of Surgery to Preventive Medicine” at the University of London’s Health Clark Lecture series, surgery has been neglected as a component of public health.^{7,76} The World Bank, in the 2006 *Disease Priorities, 2nd edition*, included its first chapter on surgery. An entire volume dedicated to surgical care is planned for the 3rd edition. There are three significant developments helping to accelerate the integration of surgery and public health:

1. Improved understanding of the burden of surgical disease and its significant component of the overall burden of global disease;
2. Recognition that surgery has a primary, secondary, and tertiary preventative role; and
3. Documentation that surgical care can be cost-effective for community-based healthcare.

Assigning Disease Priorities. Global surgery interventions can be prioritized to identify those conditions in which clinicians and public health professionals should collaborate most closely—targeting those diseases that impose the largest burden on a society and have a highly successful surgical outcome (Table 49-3).^{69,77} Levels defining public health burden, success, and feasibility have not been precisely defined. However, four broad, high-priority areas where surgery has an important role for public health interventions include: trauma care; obstetrical emergencies; acute-surgical emergencies; and nonacute surgical conditions that significantly affect the quality of life (Table 49-4).¹⁰

Trauma Care. The Essential Trauma Care Project (EsTC) begun in 2001 is a collaboration effort between the International Association for Trauma Surgery and Intensive Care, an integrated society within the International Society of Surgery-Societe-Internationale Chirurgie (ISS-SIC) and the World Health Organization (WHO), specifically the Violence and Injury Prevention unit. The project culminated in a document that identified 11 core Essential Trauma Care services (identified as the “rights of the injured patient”) that should be available at all levels of healthcare facilities (Table 49-5).⁷⁸ In addition, the document delineated 260 human and physical resources that should be available based on the type of facility (Table 49-6).

The EsTC recommendations provide a cost-effective framework for LMICs to improve their trauma care. These recommendations have been used as a planning guide and as an advocacy statement. To catalyze strengthening trauma and

Table 49-2

Ten basic and essential objectives for safe surgery (WHO*)

1. Operate on the correct patient at the correct site
2. Use method known to prevent harm from anesthetic administration, while protecting the patient from pain
3. Recognize and effectively prepare for life-threatening loss of airway or respiratory function
4. Recognize and effectively prepare for risk of high blood loss
5. Avoid inducing any allergic or adverse drug reaction known to be a significant risk for the patient
6. Consistently use method known to minimize risk of surgical site infection
7. Prevent inadvertent retention of instruments or sponges in surgical wounds
8. Secure and accurately identify all surgical specimens
9. Effectively communicate and exchange critical patient information for the safe conduct of the operation
10. Establish routine surveillance of surgical capacity, volume, and results

*WHO: World Health Organization.

Data from WHO Guidelines for Safe Surgery 2009 http://whqlibdoc.who.int/publications/2009/9789241598552_eng.pdf.

Surgical Safety Checklist		
Before induction of anaesthesia	Before skin incision	Before patient leaves operating room
(with at least nurse and anaesthetist)	(with nurse, anaesthetist and surgeon)	(with nurse, anaesthetist and surgeon)
Has the patient confirmed his/her identity, site, procedure, and consent? <input type="checkbox"/> Yes	<input type="checkbox"/> Confirm all team members have introduced themselves by name and role.	Nurse Verbally Confirms: <input type="checkbox"/> The name of the procedure <input type="checkbox"/> Completion of instrument, sponge and needle counts <input type="checkbox"/> Specimen labeling (read specimen labels aloud, including patient name) <input type="checkbox"/> Whether there are any equipment problems to be addressed
Is the site marked? <input type="checkbox"/> Yes <input type="checkbox"/> Not applicable	<input type="checkbox"/> Confirm the patient's name, procedure, and where the incision will be made.	
Is the anaesthesia machine and medication check complete? <input type="checkbox"/> Yes	Has antibiotic prophylaxis been given within the last 60 minutes? <input type="checkbox"/> Yes <input type="checkbox"/> Not applicable	
Is the pulse oximeter on the patient and functioning? <input type="checkbox"/> Yes	Anticipated Critical Events To Surgeon: <input type="checkbox"/> What are the critical or non-routine steps? <input type="checkbox"/> How long will the case take? <input type="checkbox"/> What is the anticipated blood loss? To Anaesthetist: <input type="checkbox"/> Are there any patient-specific concerns? To Nursing Team: <input type="checkbox"/> Has sterility (including indicator results) been confirmed? <input type="checkbox"/> Are there equipment issues or any concerns?	To Surgeon, Anaesthetist and Nurse: <input type="checkbox"/> What are the key concerns for recovery and management of this patient?
Does the patient have a: Known allergy? <input type="checkbox"/> No <input type="checkbox"/> Yes Difficult airway or aspiration risk? <input type="checkbox"/> No <input type="checkbox"/> Yes, and equipment/assistance available Risk of >500ml blood loss (7ml/kg in children)? <input type="checkbox"/> No <input type="checkbox"/> Yes, and two IVs/central access and fluids planned	Is essential imaging displayed? <input type="checkbox"/> Yes <input type="checkbox"/> Not applicable	

This checklist is not intended to be comprehensive. Additions and modifications to fit local practice are encouraged.

Based on the WHO Surgical Safety Checklist
http://whqlibdoc.who.int/publications/2009/9789241598590_eng_Checklist.pdf
 © World Health Organization 2009 All rights reserved

Figure 49-22. Surgical safety checklist. (WHO surgical safety checklist. 2009, http://whqlibdoc.who.int/publications/2009/9789241598590_eng_Checklist.pdf. © World Health Organization 2009 All rights reserved.)

emergency care in low-and middle-income countries, in 2007, the World Health Assembly (WHA) adopted a resolution on Emergency Care Systems (Resolution WHA 60.22).^{79,80} This first-ever WHA resolution dedicated specifically to trauma care highlights the importance accorded by world governments in caring for their injured.

Obstetrical and Other Acute Surgical Emergencies. Reduction of maternal deaths and long term disability are high priorities for the international community.⁸¹ Despite the 47% reduction in maternal deaths from 1990 to 2010, many women—mostly

in LMICs—still die daily from preventable causes related to pregnancy and childbirth.⁸² The global maternal mortality ratio (the number of maternal deaths per 100,000 live births) declined by only 3.1% per year which is significantly less than the 5.5% reduction necessary to achieve MDG 5—to decrease maternal mortality by 75% by 2015.⁸² For every maternal death, 30 women are incapacitated by chronic problems that reduce their quality of life and ability to care for their families. High priority surgical procedures to improve maternal health include Cesarean-section, hysterectomy for postpartum bleeding and uterine rupture, management of ectopic pregnancy, and dilatation and curettage.⁷⁷

About 90% of other acute surgical emergencies could be addressed by developing the capability to care for the 10 most common acute surgical conditions in any local region. While a few types of disease processes vary by geographical location, there are many that are universal, including appendicitis, strangulated hernia, small bowel obstruction, perforated peptic ulcer, fractures, lacerations, and wounds.

Nonacute Surgical Conditions. Even common nonacute conditions can have significant impact on the quality of life. Hernias can prevent otherwise healthy individuals from working, especially in societies where the economy relies heavily on manual labor. Cleft lip and cleft palate deformities interfere with the ability to speak or eat properly and predispose affected individuals to chronic ear infections leading to hearing loss. Many live in isolation because social ostracism prevents them from attending school, marrying, or holding jobs.⁸³ Plastic surgeons who pioneered global outreach for reconstructive procedures for

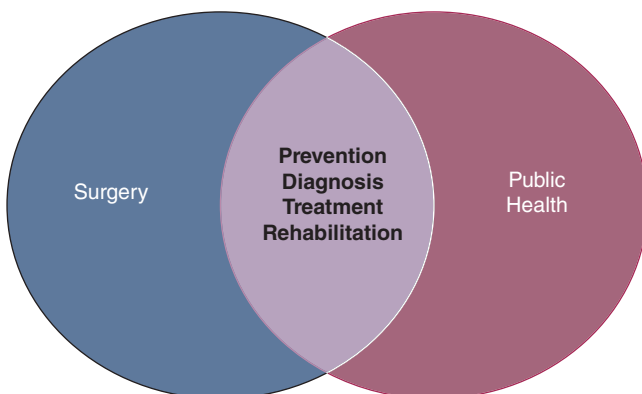


Figure 49-23. Overlapping priorities of surgery and public health. (Illustration reproduced with permission from Intermountain Healthcare.)

Table 49-3

Prioritization of surgical conditions

PRIORITY*	PUBLIC HEALTH BURDEN	SURGICAL PROCEDURE SUCCESSFUL	COST-EFFECTIVE AND FEASIBLE TO PROMOTE GLOBALLY
1	High	Highly	Highly
2	Moderate	Moderately	Moderately
3	Low	Neither highly or moderately	Low

*Priority one implies that all three conditions must be met. The priority should be shifted to 2 or 3 if any of the conditions are moderate or low.

Data adapted from: Mock C, et al. Developing priorities for addressing surgical conditions globally: furthering the link between surgery and public health policy. *World J Surg.* 2010;34(3): 381–385.

cleft lip and palate opened the door for subsequent outreach by other specialties, including ophthalmology, orthopedics, general surgery, urology, and dentistry.⁸⁴⁻⁸⁶

The most common form of blindness is caused by cataracts. Cataracts decrease the quality of life and the socioeconomic status for both the blind person and his family. The fact that 90% of blind people no longer work, places extra burdens on the family members who care for them.⁸⁷ The Himalayan Cataract Project (HCP) is a highly successful initiative focusing on cataracts in Asia and Africa. HCP priorities and measurable outcomes illustrates how combining key public health concepts with a comprehensive approach to surgical care creates a model for curing disease, building economies, and delivering hope in resource-poor areas.⁹ (**Box:** The Himalayan Cataract Project: A Sustainable Public Health Approach for Curing Blindness)

Cancer Initiatives

Surgery for cancer in public health plays a role not only for curative surgery, but also for early diagnosis, prevention, and

palliation.^{19,91-93} Solid tumors, in their early stages, presents insidiously as a nonacute surgical problem. Due to cancer's recent recognition as a leading cause of death, cancer has been identified as a health priority in LMICs. Most solid tumors are incurable without surgery and at a minimum require surgical excision of the primary lesion.⁹¹

It is often not appreciated that surgeons provide a significant amount of primary care and are the principle providers involved in endoscopic screening and treatment of gastrointestinal tumors in LMICs. In countries without specialized services, low-cost and effective treatment options combining early prevention and treatment with off-patent drug use have led to coverage of cancer treatment in several middle-income countries' national health insurance plans.¹⁹ Cancer care provides significant opportunity for including surgery in community-wide public health programs as a high priority according to the prioritization model; cancer has a high public health burden, is treated with highly successful procedures, and can be cost-effective and feasible globally. In 2009, a coalition of leaders in cancer care and public health organized the Global Task Force on Expanded Access to Cancer Care and Control in Developing Countries (GTFCCC)⁹⁴ GTFCCC's mission is to expand access

Table 49-4

The role of surgery for public health strategies

Trauma care	Prevention of death and chronic disability by the provision of timely, expert, and complete surgical care
Obstetrical emergencies	Timely surgical intervention in obstructed labor, in pre- and post-partum hemorrhage, and other obstetrical complications
Acute surgical emergencies	Provision of competent surgery to treat a wide range of emergency abdominal and nonabdominal conditions
Nonacute surgical conditions	Surgical care for several elective conditions that have a significant effect on the quality of life such as cataract, otitis media, clubfoot, and hernias

Data adapted from Debas, HT, et al, *Surgery, in Disease Control Priorities in Developing Countries*. 2nd ed. Jamison DT, Breman JG, Measham AR et al (eds.) New York: Oxford University Press for The World Bank, 2006, p. 1245–59.

Table 49-5

Essential trauma care services

1. Obstructed airway appropriately maintained
2. Impaired breathing supported
3. Pneumothorax and hemothorax promptly diagnosed and treated
4. Bleeding promptly stopped (internal or external)
5. Shock recognized and treated appropriately (I.V. fluids)
6. Timely decompression of space occupying lesions to prevent secondary brain injury
7. Abdominal injuries diagnosed and promptly repaired (intestinal injuries and others)
8. Disabling extremity injuries corrected
9. Potentially unstable spine injuries identified and managed (early immobilization)
10. Minimize consequences of injuries by appropriate rehabilitative services
11. Medication to provide above services and relieve pain readily available

Data adapted from Mock C, Joshipura M, Goosen J, Maier R. Overview of the Essential Trauma Care Project. *World J Surg.* 2006;30(6): 919–929.

Table 49-6

Airway management recommendations for physical and human resources based on type of facility (sample from EsTC*)

KNOWLEDGE AND SKILLS	FACILITY LEVEL			
	BASIC	GENERAL PRACTITIONER	SPECIALIST	TERTIARY
Assessment of airway compromise	E	E	E	E
Manual maneuvers (chin lift, jaw thrust)	E	E	E	E
Insertion of oral or nasal airway	D	E	E	E
Endotracheal Intubation	D	D	E	E
Equipment and supplies				
Oral or nasal airway	D	E	E	E
Laryngoscope	D	D	E	E
Endotracheal tube	D	D	E	E
Capnography	I	D	D	D

E: essential; D: desirable; I: irrelevant (not usually to be considered at the level in question).

*EsTC: Essential Trauma Care.

Data adapted from Mock C, Lormand JD, Goosen J, Joshipura M, Peden M. *Guidelines for essential trauma care*, 2004, Geneva: World Health Organization, p. 21.

The Himalayan Cataract Project (HCP): A Sustainable Public Health Approach for Curing Blindness

According to the WHO criteria, 180 million people worldwide are visually disabled. Of that population, 45 million are classified as bilaterally blind; 90% live in the developing world where poor water quality, lack of sanitation, malnutrition, and inadequate services cause a higher incidence of eye disease.⁸⁷ The most common cause of avoidable blindness in LMICs is cataract (50%). Nepal has one of the highest incidences of cataracts due to increased exposure to ultraviolet sunlight encountered at its higher elevations; 70% of curable blindness in Nepal is due to cataracts.⁸⁸

In 1995, Sanduk Ruit joined forces with Geoffrey Tabin to establish the Himalayan Cataract Project (HCP). In the early 1990's, difficult geography and lack of transportation, the cost of the intraocular lens, and lack of trained ophthalmologists, assistants, and nurses limited access to cataract surgery for the poor.

HCP developed and defined six priorities each with an associated public health principle and outcome measurements that provided the basis for assessing success and for implementing change (Fig. 49-24). HCP's care model targeted the entire population of blind people with cataracts regardless of the ability to pay. Since most of the potential patients lived in remote areas, HCP found it imperative to take cataract surgery to the local communities. The Tilganga Institute of Ophthalmology (TIO) in Katmandu, Nepal, has served as a base from which over 100 doctors and 100 ophthalmic assistants and nurses have been trained.⁸⁹ Through the TIO and its outreach programs, over 2,573,000 people have been screened and more than 172,000 eye surgeries have been performed since 1994 (Fig. 49-25).⁸⁹

The TIO developed an ophthalmology residency training program implementing standards set forth by the American Academy of Ophthalmology. In addition to the formal residency program for ophthalmologists, HCP established training programs for community eye care workers in a three-year Ophthalmic Assistant Training Program.

Ruit developed an innovative suture-less technique for cataract surgery yielding equivalent results to those in developed countries but also reproducible in resource-constrained areas. By redesigning the intraocular lens and mass producing it locally in Nepal for U.S. \$4.00, Ruit and Tabin provided a low cost alternative to the higher-priced lens produced in developed countries. A local business—the Fred Hollows Intraocular Lens Factory—mass produces the lenses and helps support the local economy by introducing a new sustainable business locally.⁹⁰

HCP also designed a socially acceptable method for cost-recovery that involves a sliding scale for payment: 45% of patients pay U.S. \$120.00; 20% pay a smaller amount based on their economic situation; and 35% receive cataract surgery for free.

HCP Priorities	Public Health Principles	Implementation
Humanitarian	Accessible	Entire Population Care at Local Level
High Quality	Appropriate	Care Comparable to Western Standards Disease with High Incidence/Prevalence
Innovation	Disruptive Technology	Designed \$4 lens Local Business
Direct Impact	Sustainable Growth	Skills Transfer Building Infrastructure
Affordability	Affordable	Delivery Model \$20 Cost/Cataract
Replication	Sustainability	Meet Needs of Current Population Culturally and Economically Acceptable

Figure 49-24. Himalayan cataract project priorities, public health principles, and outcome measurements. (Redrawn from *Himalayan Cataract Project and Tilganga Eye Center*, (Cureblindness.org) (82-84) by permission. Illustration reproduced with permission from Intermountain Healthcare.)

to cancer prevention, detection, and care in LMICs. Successful partnerships have already been entered into Haiti, Rwanda, Mexico, Malawi, and Jordan.

The Preventive Role of Surgery. Surgery plays a significant role at all levels of prevention of disease (Table 49-7). Trying to disassociate treatment from prevention presents challenges. Treatments can also be a form of prevention. For example, one of the root causes for the development of a vesico-vaginal fistula is lack of access to appropriate peri-partum care. Expediently performing a Cesarean-section (a form of secondary prevention) for obstructed labor primarily prevents the

development of vesico-vaginal fistulas (primarily preventing the development of a different disease).

The surgeon's role for disease prevention in the developing world is in its infancy of realization. Diseases commonly present in very late stages in LMICs and in disadvantaged populations in developed countries. Many morbid conditions could have been cured while localized in their earlier stages and likely eradicated by a local surgical procedure. Early recognition and treatment of surgically correctable diseases is a critical preventive role for surgery. Many surgical procedures are not only a form of tertiary prevention, but are also forms of primary prevention (Table 49-8).⁹¹

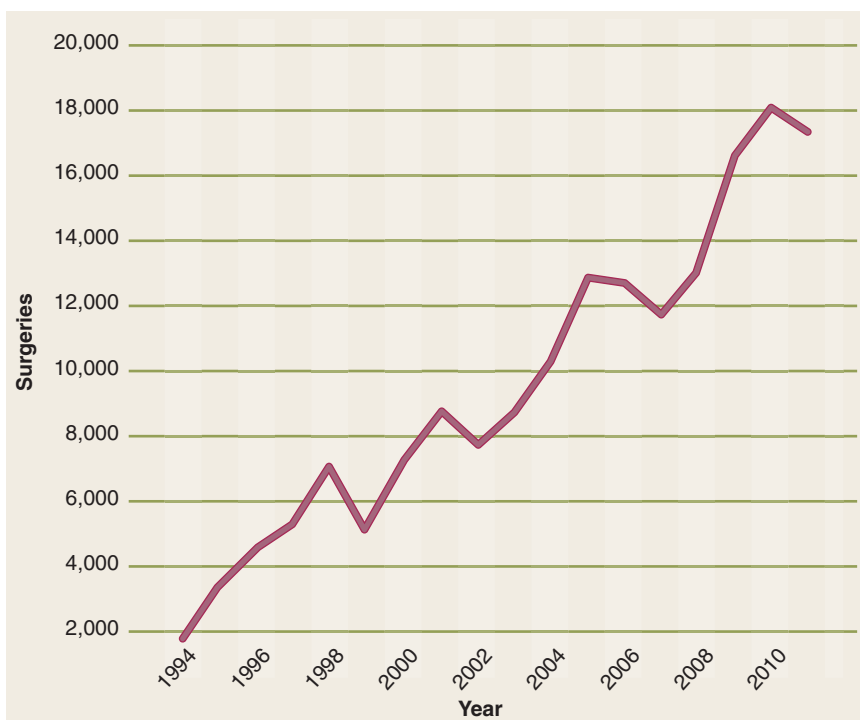


Figure 49-25. Eye surgeries Tilganga eye center and outreach. (Redrawn from *Himalayan Cataract Project and Tilganga Eye Center*, (Cureblindness.org) (82-84) by permission. Illustration reproduced with permission from Intermountain Healthcare.)

Table 49-7

Prevention strategies

PREVENTION STRATEGY	TARGET	GOAL
1. Primary	Root causes of disease	Eliminate or reduce risk of developing illness
2. Secondary	Illness or disease at earliest stages	Limit progression of disease
3. Tertiary	Disease at later stages	Cure or limit the effect of existing disease

Data adapted from deVries, C. and R.R. Price. *Global Surgery and Public Health: A New Paradigm*. 1st ed, 2012, Sudbury, MA: Jones & Bartlett Learning, LLC, p. 43-45.

Cost-effectiveness of Surgical Care. Funders in healthcare look for measurable return on their investments. While comparison of outcomes and objective measures would be ideal, reality demonstrates that healthcare budgets more commonly are dictated by politics rather than actual need. Nevertheless, in a world of limited resources and tightening budgets for healthcare, cost-effective analysis of various options for intervention are critical for policy makers. Comparing various options that have different outcomes is an approach called cost-utility analysis (CUA). Surgical interventions can be evaluated by specific diseases or conditions, or by systems or services required to support the delivery of surgical care. In 1990, the World Bank defined the Disability Adjusted Life Year (DALY) as the sum of Years of Life Lost (YLL) due to premature mortality in the population and the Years Lost due to Disability (YLD) for people living with the health condition or its consequences. (DALY = YLL + YLD). Evaluating the cost per DALY averted is one approach for comparing the cost-utility between medical and surgical interventions. Recent surgical cost/DALY studies identifying the cost-effectiveness of various types of

10►

Table 49-8

The role of surgery for primary prevention of cancer

TERTIARY SURGICAL PROCEDURE	PRIMARY CANCER PREVENTED
Breast lumpectomy for ductal carcinoma in situ	Breast
Colonoscopic polypectomy	Colon
Colposcopy and excision	Cervical
Resection of actinic keratosis	Skin
Resection of leukoplakia and erythroplakia	Oral

Data adapted from Riviello R, Meara JG, Rogers SO. Commentary: Cancer Care and Control - the role of surgery. *Global Surgery and Anesthesia*. 2010. Retrieved February 20, 2013, from <http://www.ghdonline.org/surgery/discussion/cancer-care-and-control-the-role-of-surgery/>

surgical care have allowed surgical initiatives to be considered when prioritizing public health initiatives.

The World Bank arbitrarily defined U.S. \$100/DALY averted per day in low-income countries as highly cost-effective. Compared to other public health initiatives, developing basic and emergency surgical care at the district level hospital is as cost-effective as or more so than typical public health programs such as retroviral treatments for HIV/AIDS or immunization for measles (Table 49-9).⁹⁵⁻⁹⁹

Using the WHO's cost-effectiveness standards, investing in emergency obstetrical systems, including timely Cesarean delivery can also be considered "highly cost-effective" for 48 of 49 countries in which there are currently inadequate numbers of Cesarean deliveries^{100,101}. The median cost per DALY averted by Cesarean-section was \$304. In addition, the cost-benefit ratio in 46 of 49 countries was >1, suggesting that investment in Cesarean delivery is a viable economic proposition.

Table 49-9

Cost effectiveness of public health measures

PUBLIC HEALTH INTERVENTION	COST-EFFECTIVENESS (U.S. \$/DALY* AVERTED)
Rapid impact package for neglected tropical diseases	2-9 ^a
Measles vaccination	5 ^a
Basic surgical services district hospital	11-33 ^a
Antiviral therapy for HIV	300-500 ^a
Lichtenstein hernia repair with mosquito net mesh Western Ghana	12 ^b
Lichtenstein hernia repair with polypropylene or mosquito net Ecuador	78 ^c
Emergency systems for Caesarean delivery	304 ^d
Cataract surgery	57 ^e

*DALY: Disability Adjusted Life Year

(a. Ozgediz D, Riviello R. The "other" neglected diseases in global public health: surgical conditions in sub-Saharan Africa. *PLoS Med*. 2008; 5(6):e121; b. Shillcutt SD, Clarke MG, Kingsnorth AN. Cost-effectiveness of groin hernia surgery in the Western Region of Ghana. *Arch Surg*. 2010;145(10):954-961; c. Shillcutt SD, et al. Cost-effectiveness of inguinal hernia surgery in northwestern Ecuador. *World J Surg*. 2013;37(1):32-41; d. Alkire BC, et al. Obstructed labor and caesarean delivery: the cost and benefit of surgical intervention. *PLoS One*. 2012;7(4): e34595; e. Baltussen R, Sylla M, Mariotti SP. Cost-effectiveness analysis of cataract surgery: a global and regional analysis. *Bull WHO*. 2004;82:338-345.)

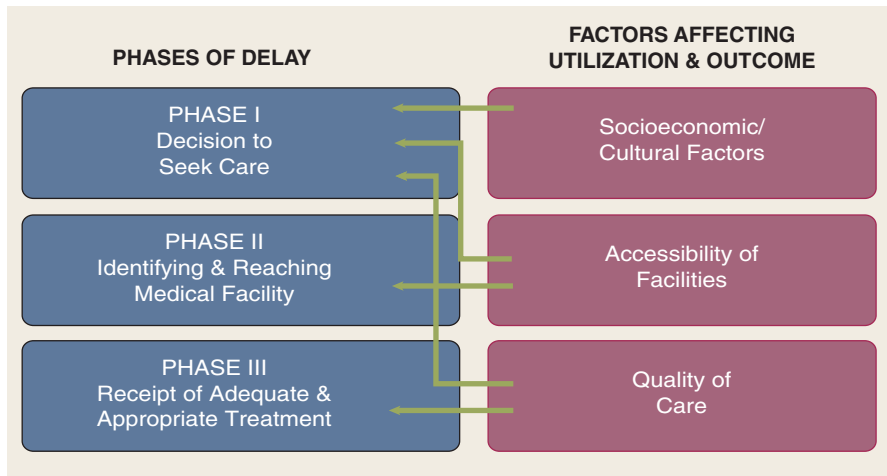


Figure 49-26. Factors affecting utilization and outcome of surgical care. (Adapted from UNFPA United Nations Population Fund (UNFPA); *Providing emergency obstetric and newborn care to all in need*. [cited 2013 February 27]; Available from: <http://www.unfpa.org/public/mothers/pid/4385>. Illustration reproduced with permission from Inter-mountain Healthcare.)

Inguinal hernia repair is one of the most common operations performed worldwide. Tension-free inguinal hernia repairs performed with mosquito netting or polypropylene mesh was cost-effective in Western Ecuador and Western Ghana (\$78.18/DALY and \$12.88/DALY averted, respectively).^{96,102} Using mosquito netting in India was 3700 times cheaper than using traditional polypropylene mesh.¹⁰³

Factors Affecting Utilization and Outcome for Surgical Care. There are three major factors that severely limit utilization of surgical services:

1. socioeconomic and cultural
2. accessibility of facilities and
3. quality of care (Fig. 49-26)¹⁰⁴

The decision to seek timely care is affected by the costs associated with time off from work and inability to support the family during the absence, transportation and lodging, and the surgical services themselves. Cultural and religious traditions may define acceptability of various treatment options. For example, many people in Mongolia refuse to have surgery on Tuesdays as this is viewed as a “bad luck” day. Understanding local customs and cultural concerns can improve utilization of surgical services.

Austere environments, difficult terrain, and long distances from health care facilities significantly delay or prevent access to surgical care. Triage and transfer guidelines along with telemedicine have the potential to mitigate the limitations of geography. However, without adequately trained care providers and support staff, the risk for poor outcomes is increased.

Recognizing these three important factors for increasing utilization and outcomes, Mongolia initiated a public health approach for the management of gallbladder disease incorporating minimally invasive surgery. (**Box:** The Public Health Approach to Management of Gallbladder Disease in Mongolia)

The Public Health Approach to Management of Gallbladder Disease in Mongolia

Mongolia, the most sparsely populated country in the world, covers a large geographic area nestled between China and Siberia.¹⁰⁵ The austere environment with extremes of weather, dry deserts, and high mountains present significant obstacles for road building limiting transportation for patients

in the vast rural areas (Fig. 49-27). Significant deficiencies in infrastructure, supplies, equipment, and human resources at primary healthcare facilities exist: sporadic electricity, no fully qualified surgeons or anesthesiologists, and less than half the facilities with running water.³ In 2006, Healthcare expenditures reached only U.S. \$23.2 per capita.^{106,107}

The second most common cause of inpatient morbidity in Mongolia has transitioned to gastrointestinal diseases with liver disease, appendicitis, and gallbladder disease the top three causes.¹⁰⁸ While laparoscopic cholecystectomy was introduced in Mongolia in 1994, by 2005 only 2% of gallbladders were removed laparoscopically, and then, only in the capital city.¹⁰⁹ A cohort study in 2005 comparing open with laparoscopic cholecystectomy by Dr. Sergelen, the chief of surgery at the Health Sciences University of Mongolia (HSUM), found the wound infection rate to be significantly lower, hospital stays shorter, and hospital expenditures 50% less with laparoscopy compared to open cholecystectomy.¹¹⁰ Dr. Sergelen formulated a plan to expand access to laparoscopic surgery throughout Mongolia. This plan targeted the three main areas affecting utilization and outcome.

- a) **Quality of Care** Develop a laparoscopic training didactic and practical course to train surgical teams.
- b) **Accessibility of Quality Care** Begin training surgical teams in the capital city, but then expand them to four carefully selected regional diagnostic treatment and referral centers (RDTRCs) in all four quadrants of the country.
- c) **Quality of Care** Improve the surgical infrastructure for each facility.
- d) **Socioeconomic/Cultural Factors** Educate the public on the increased benefits of laparoscopic surgery so they would initiate lobbying efforts demanding the government increase funding for these services.
- e) **Socioeconomic/Cultural Factors** Educate government leaders about the need and benefit of laparoscopic cholecystectomy for the Mongolian people.
- f) **Quality of Care** Expand the surgical residency to include laparoscopic training.
- g) **Accessibility and Quality** Invite industry to offer cost-affordable supplies and replacement parts to sustain the laparoscopic equipment in Mongolia.



Figure 49-27. Rural Ger. (Photo reproduced with permission from Michelle K. Price.)

Laparoscopic cholecystectomy has been expanded within the capital city and established in the initial 4 key Regional Diagnostic and Treatment Referral Centers (RDTRCs) and an additional fifth regional hospital creating countrywide access to high-quality modern surgery for a regionally prevalent disease through a multinational partnership directed by the chief of surgery at HSUM (Fig. 49-28).^{105,111}

As people began to see their neighbors return to functional ability faster with the laparoscopic approach, the Mongolian people developed increased trust in their healthcare

providers and the quality of care they could receive. This led to not only an increase in laparoscopic cholecystectomy but an increase in open cholecystectomy and many other procedures (Fig. 49-29).¹⁰⁵

The Mongolian surgical residency has been expanded to incorporate laparoscopic training. The MOH has committed to increase funding for laparoscopic cholecystectomy and change existing laws making it easier for hospitals to purchase their needed supplies.



Figure 49-28. Regional diagnostic treatment and referral centers of Mongolia (RDTRCs). (Illustration reproduced with permission from Intermountain Healthcare.)

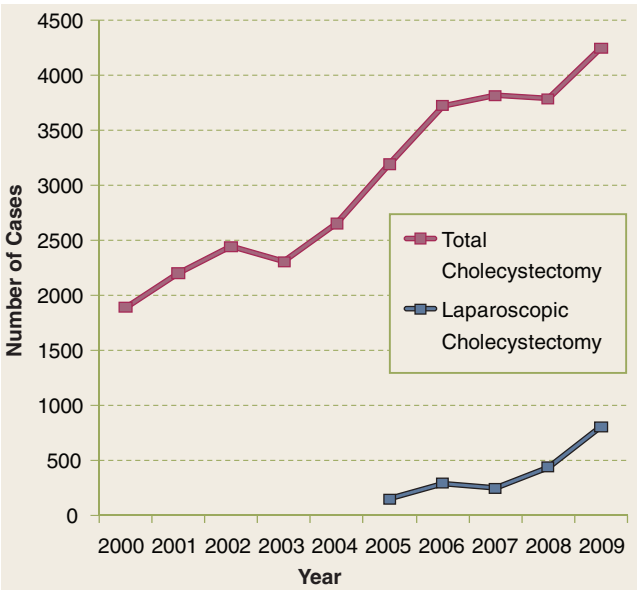


Figure 49-29. Cholecystectomy trends in Mongolia. (Adapted from: Unursaikhan C. (2010). Information of biliary track surgery in Mongolia. Health Sciences University of Mongolia, unpublished data. Illustration reproduced with permission from Intermountain Healthcare.)

Advanced Surgical Care for Resource-Poor Areas

Limited financial, physical, and human resources, political and social conflicts, and austere environments cause many to believe that advanced surgical care is inappropriate in resource poor countries.^{77,112-114} Misconception of the needs and abilities

11▶ of people in LMICs cause some policy makers to discount the desire of people worldwide for advanced surgical care.¹⁰⁵ Developing these capabilities in resource-poor countries has the potential to decrease overall cost and actually develop the infrastructure necessary to entice physicians and other healthcare workers to remain in their own countries. Establishing advanced surgical care requires expertise and services that symbiotically support and improve general medical care. Therefore, many developing countries are actively building capacity and capability to provide the full spectrum of modern surgical care locally.¹¹⁵

As economies improve and the benefits of laparoscopic surgery for resource-poor areas become better delineated, patients and doctors, surgical societies, ministries of health, and industries are demanding the benefits of minimally invasive surgery for patients and communities.^{111,116-122} The economic impact of laparoscopy may be even greater in LMICs than in developed countries.¹²³ Worldwide surgeons have identified laparoscopic training as one of their greatest needs. In a recent survey, developing laparoscopic and endoscopic skills were identified as the most important skills desired by surgeons from the West Africa College of Surgeons (WACS) (Fig. 49-30).¹²⁴

Transplantation is another area of great interest to people in poor countries partly because of the high prevalence of kidney failure and because chronic dialysis facilities are limited. Hepatoma and liver failure are very common in countries with a strong prevalence of hepatitis B and C. Transplantation has become the treatment of choice for end-stage kidney disease in developed countries as it dramatically improves the quality of life and increases survival rates compared to medical management.¹²⁵ Yet, transplantation eludes most of the developing world. Initial attempts to transport critically ill patients from LMICs to developed countries for kidney transplantation were

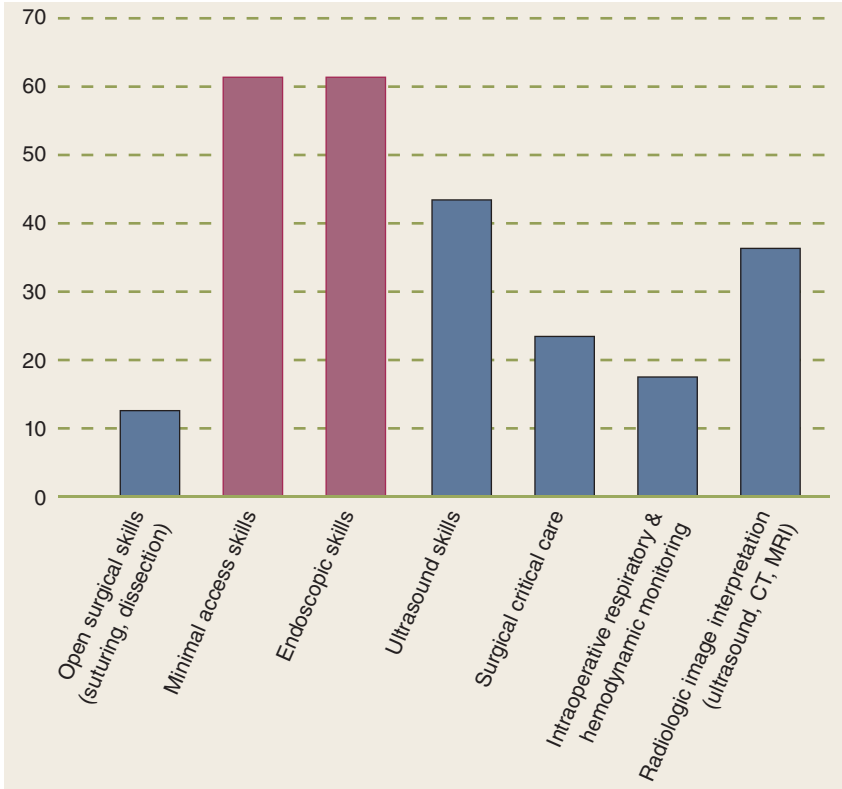


Figure 49-30. West African College of Surgeons: most desired skills. (Adapted from Trigen Survey WACS: Akporiaye L. (2010). Trigen Survey: West African College of Surgeon. Port-Harcourt: Unpublished data. Illustration reproduced with permission from Intermountain Healthcare.)

cost-prohibitive.¹²⁶ With the alarming increase in the rate at which young people have been presenting with kidney disease in developing countries, the increased utilization placed on the few dialysis machines has been overwhelming.¹²⁷ Dialysis units which previously were utilized three times a week, now operate 24 hours a day, 7 days a week, and cannot begin to provide the needed services to the multitudes needing treatment. Even programs to develop peritoneal dialysis cannot fully ease the demand.

The majority of kidney transplants in developing countries are from living related donation. Laparoscopic living related donation has the potential to increase the voluntary donor pool as patients have less postoperative pain, return to work and activities quicker, and have much better cosmesis than open surgery.¹²⁸ Adapting to the limited resources, surgeons have described various cost-saving techniques to facilitate the laparoscopic approach in resource poor areas such as using endoclips instead of staplers for vascular control, modifications to the surgical approach, and suprapubic extraction of the kidney rather than endocatch removal.¹²⁸⁻¹³⁰

Academic Partnerships

Academic institutions have historically pioneered discovery in disease causation and treatment. As globalization expands, academic surgical programs are beginning to respond by broadening their vision for an interdisciplinary and collaborative approach to research, education, development, and advocacy.¹³¹⁻¹³²

12► Academic involvement in global surgery provides training for the next generation of surgical leaders. Leaders for the 21st century will need to know how to provide outstanding cost-effective clinical care for all environments. With a more global view, the significant advances in scientific knowledge and clinical practice realized through basic and clinical research will potentially provide solutions for access to surgical care for all patients worldwide. Partnering academic programs with NGOs provides another opportunity for collaboration. **(Box: Academic Global Surgery Partnerships)**

Ethics

The ethics involved in working outside one's own home country are complex. While a practitioner's scope of practice is usually constrained by regulation in America and Europe, in many countries the limits of what one can do are neither regulated nor enforced. Guidelines for what should be done—where, and under what circumstances are beyond the expertise of some ministries of health. Some problems are so episodic that they are not anticipated, and few guidelines exist. For example, in natural disasters and emergencies, should any willing provider from any country be granted permission to provide care? Should specific disaster-related training be encouraged or required?^{134,135} In the

research, and mentoring throughout the length of their surgical residency at BWH. During the research years, GHE residents engage in collaborative field-based programs and research that link and support many of BWH global surgery activities. Projects to date include: Understanding Trauma Epidemiology in Rwanda, Understanding Surgical Epidemiology of Burera District, Cost-Effectiveness analysis of the Team Heart global cardiac surgery program, and Breast cancer epidemiology of Rwanda.¹³³ —Robert Riviello MD

B. Rwanda Human Resources for Health (HRH) Program

“The Rwanda HRH program is an ambitious 7-year long, U.S. federally funded, collaborative program of the Rwanda Ministry of Health (MOH) and 13 U.S. academic medical centers and universities. HRH seeks to greatly expand and improve Rwanda's health care workforce by strengthening national training programs of specialized physicians, nurses, oral health providers, and hospital managers by recruiting U.S. faculty educators to join the National University of Rwanda (NUR) training faculty. In year one of the program (August 2012–July 2103), BWH contributed the largest number of physician educators to the program, recruiting 40% of the U.S. HRH physician faculty, including 6 surgeons. These surgeons have worked closely with their Rwandan faculty counterparts to restructure and organize the NUR surgery residency program, including development of curriculum, organizing didactic and clinical teaching, and greatly strengthening resident supervision and mentorship¹³³.” —Robert Riviello MD

C. Coordinating Non-Governmental Organizations (NGO) and Academic Organizations: IVUmed

Nonprofit organizations (NGO) have filled a niche in establishing surgical care in countries where training centers and healthcare systems are historically non-existent or understaffed. More recently, professional organizations have developed a focus on specific diseases or patient groups and have become a resource for education and training in poor countries.

For more than 20 years, the IVUmed NGO has focused on urological education and hands-on training in Africa, Asia, and Latin America. IVUmed evolved from a need identified by plastic surgeons that had seen many children with hypospadias and other urological anomalies such as exstrophy, when providing care for children with cleft lip and palate. Adult surgeons were not trained in the delicate reconstruction of pediatric genitourinary anomalies, and pediatric surgeons were not trained in endoscopic or reconstructive urological surgery. The program has expanded to support training in all aspects of urological care, including adult reconstruction, oncology, and endoscopic management of stones and prostatic disease.

As a nonprofit organization, IVUmed is a partnership between surgeons, anesthesiologists and nurses, academic medical centers, urological professional associations, industry and the public with urologic surgery training in more than 20 countries. It also provides North American trainees scholarships to travel to low-resource countries to learn and to share knowledge gained in their own programs. Many former scholars become mentors for other residents when they complete their training. The sites with the longest collaborations have developed their own educational programs in general urology or subspecialty areas and are now providing advanced training and care locally (Fig. 49-31).

Academic Global Surgery Partnerships

A. Global Health Equity Residency

“In 2012, Brigham and Women's Hospital (BWH) Center for Surgery and Public Health (CSPH) launched the Global Health Equity in Surgery (GHE-S) residency program. Related to its sister program in Internal Medicine at BWH, the GHE-S program seeks to create future leaders in academic global surgery through structured education, field work,

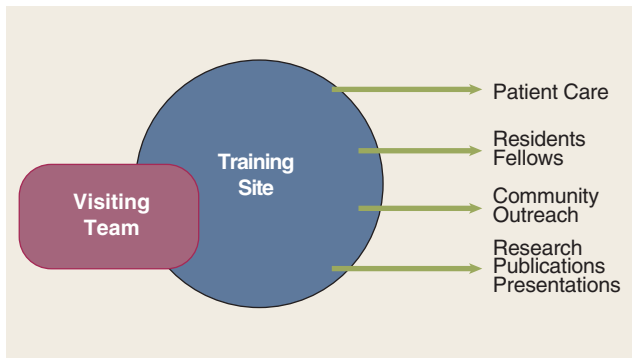


Figure 49-31. Training outcomes from NGO/academic partnership. (Reproduced with permission from IVUmed and Intermountain Healthcare.)

non-acute setting, should practitioners not licensed or credentialed in their home environments be allowed to perform volunteer surgery in other countries? What entity should oversee the flow of volunteer practitioners? Can a standard set of guidelines meet the needs of most countries? Currently, there is little cross national agreement between state entities, like ministries of health and independent organizations and individuals. While many countries require at least temporary licensure, some do not. In many cases enforcement is inconsistent.

With respect to research, the poor historically have not received benefit from research performed on them. In international studies, even local collaborators have been left out of study design and publication.¹³⁶ As Internet communications have improved, these lapses no longer are tolerated.¹³⁷ Informed consent for surgical procedures, given in the appropriate language and respectful of local customs, are becoming more the norm. Few hospitals outside academic medical centers have institutional review boards (IRBs) to oversee the implementation and review of clinical research. In recent years, peer reviewed journals have become more mindful of attribution of credit, and authors are strongly encouraged to design and report studies with local input at all levels.

With regard to transplantation, many countries have laws against cadaveric transplants because of the very real concern for illegal marketing of organs. Even living-donor transplantation has seen effects of coercion in some regions and for some populations such as prisoners. Nevertheless, the need and popular desire for transplantation is accelerating acquisition of skills and technology to make transplantation available worldwide.¹³⁸

Finally, what is considered ethical in one country or one community might be considered highly unethical in another. Consent for surgery may in one setting rest with the patient, but in another, with the community or family. And values about privacy vary markedly from region to region. Health information in many cultures is considered to be a community concern and not the personal property of an individual patient.

Innovation in Global Surgery

The pressing need for surgical care at all levels and the shortage of fully trained surgeons, anesthesiologists and support personnel, equipment and supplies means that opportunities abound for innovation. Innovations in education, including simulation, can potentially shorten the time necessary for learning technical skills. Gaming technology can potentially teach algorithms for decision making and

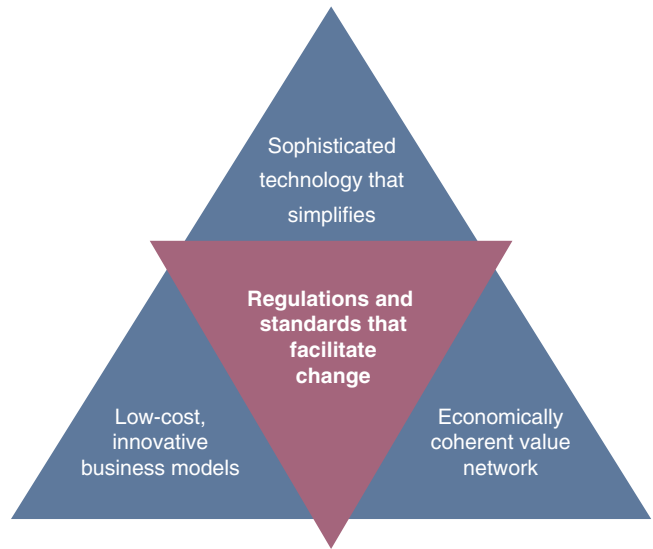


Figure 49-32. Elements of disruptive innovation. (Redrawn with permission from Christensen CM, Grossman JH, Hwang J. *The Innovator's Prescription*. New York: McGraw-Hill, 2009. Copyright © The McGraw-Hill Companies, Inc. Illustration reproduced with permission from Intermountain Healthcare.)

interpretation of X-rays and ultrasounds. Telemedicine/telehealth has the potential to transform education through combinations of clinical case-based learning and massively open online courses (MOOC). The potential for education innovation in surgery beyond the apprenticeship system championed by Halsted in 1904 is vast.

Innovation that radically changes the way we do things, that changes a paradigm of a service or system is called “disruptive”; it abruptly changes an older and more expensive system in favor of a less expensive, more widely available technology or process. The ability for disruptive innovations to transform products and services into affordable realities requires three main factors (Fig. 49-32).¹³⁹

Regulations and standards that vary between countries and locales can facilitate or impede disruptive change. While disruptions often are not qualitatively superior to the status quo, they make the process both less expensive and more accessible, and through multiple iterations, ultimately improve quality as they cycle through the transformative process.

De-centralizing education, laboratory testing, and medical records have been made possible through Free and Open Source Software, apps, and devices such as smart phones, tablets, and laptop computers. Monitoring devices, laparoscopic instruments, and imaging devices designed for low resource environments have the potential to not only improve accessibility in poor countries, but also to radically reduce surgical costs in wealthy ones.

THE FUTURE FOR GLOBAL SURGERY

Surgeons of the future will need to educate themselves in areas that have not historically been taught in surgical curricula. Beyond the business of surgical practice, there is a complex ecosystem that supports surgical care. Surgeons must become more aware of the complexities of cost in order to be able to shape the

environment in which they work. They must understand better what patients are seeking from the surgical experience rather than focusing primarily on a narrow view of what surgery might have to offer. Surgeons must engage in policy development and advocate for affordable and accessible surgical care without sacrificing quality. Thoughtful technology design can focus on improving quality and on decreasing cost, both in poor and wealthy countries. As our colleagues in public health and the World Bank, Paul Farmer and Jim Kim have challenged us, “We need our surgical colleagues to speak fluently about rebuilding infrastructure, training, personnel, and delivering high-quality care to the very poorest.”⁷

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